*Carla Maria Teixeira de Oliveira*

# Incidence of hip fractures in Portugal from 2000-2010. A spatial-temporal analysis.

*Porto – 2015*

*Carla Maria Teixeira de Oliveira*

# Incidence of hip fractures in Portugal from 2000-2010. A spatial-temporal analysis.

Dissertação de candidatura ao grau de Doutor em Saúde Pública, apresentada à Faculdade de Medicina da Universidade do Porto, realizada sob a orientação científica da Professora Doutora Maria de Fátima Rodrigues Pereira de Pina, do Departamento de Departamento de Epidemiologia Clínica, Medicina Preditiva e Saúde Pública da Faculdade de Medicina da Universidade do Porto e co-orientação da Professora Doutora Denisa Maria de Melo Vasques de Mendonça, Professora Associada Aposentada do Instituto de Ciências Biomédicas Abel Salazar e do Professor Doutor Trevor Bailey do College of Enginnering, mathematics and physical Sciences from Universidade de Exeter, UK.

***Porto – 2015***

“Never regard study as a duty but as an enviable opportunity to learn to know the liberating influence of beauty in the realm of the spirit for your own personal joy and to the profit of the community to which your later works belong.”

Albert Einstein

“Jamais considere seus estudos como uma obrigação, mas como uma oportunidade invejável para aprender a conhecer a influência libertadora da beleza do reino do espírito, para seu próprio prazer pessoal e para proveito da comunidade à qual seu futuro trabalho pertencer.”

Albert Einstein

Este trabalho foi realizado com o apoio financeiro da Fundação para a Ciência e a Tecnologia

***Porto – 2015***

Art.º 48º, § 3º - "A Faculdade não responde pelas doutrinas expendidas na dissertação."
(Regulamento da Faculdade de Medicina da Universidade do Porto – Decreto-Lei nº 19337 de 29 de Janeiro de 1931)

## Constituição Do júri Da Prova De Doutoramento

### Presidente

DOUTOR FRANCISCO FERNANDO DA ROCHA GONÇALVES,
Professor catedrático da Faculdade de Medicina da Universidade do Porto;

### Vogais

DOUTOR ENRIQUE GOMEZ-BARRENA
Professor catedrático da Hospital La Paz, IdiPaz, Universidad Autónoma de Madrid;

DOUTOR INÊS PEREIRA SILVA CUNHA SOUSA
Professora auxiliar da Escola de Ciências Universidade do Minho;

DOUTOR JOSÉ ANTÓNIO PEREIRA DA SILVA
Professor catedrático da Faculdade de Medicina da Universidade de Coimbra;

DOUTORA CARLA MARIA MOURA LOPES
Professora associada da Faculdade de Medicina da Universidade do Porto;

DOUTOR PEDRO NUNO FERREIRA PINTO DE OLIVEIRA
Professora associada do Instituto de Ciências Biomédicas de Abel Salazar da Universidade do Porto;

DOUTORA MARIA DE FÁTMA RODRIGUES PEREIRA DE PINA
Professora associada da Faculdade de Medicina da Universidade do Porto e orientadora da tese;

**CORPO CATEDRÁTICO DA FACULDADE DE MEDICINA DO PORTO**

# Corpo Catedrático da Faculdade de Medicina do Porto

## Professores Catedráticos Efectivos

DOUTOR MANUEL ALBERTO COIMBRA SOBRINHO SIMOES
DOUTORA MARIA AMELIA DUARTE FERREIRA
DOUTOR JOSÉ AGOSTINHO MARQUES LOPES
DOUTOR PATRÍCIO MANUEL VIEIRA ARAÚJO SOARES SILVA
DOUTOR DANIEL FILIPE LIMA MOURA
DOUTOR ALBERTO MANUEL BARROS DA SILVA
DOUTOR JOSE MANUEL LOPES TEIXEIRA AMARANTE
DOUTOR JOSE HENRIQUE DIAS PINTO DE BARROS
DOUTORA MARIA FÁTIMA MACHADO HENRIQUES CARNEIRO
DOUTORA ISABEL MARIA AMORIM PEREIRA RAMOS
DEOLINDA MARIA VALENTE ALVES LIMA TEIXEIRA
DOUTORA MARIA DULCE CORDEIRO MADEIRA
DOUTOR ALTAMIRO MANUEL RODRIGUES COSTA PEREIRA
DOUTOR RUI MANUEL ALMEIDA MOTA CARDOSO
DOUTOR JOSE CARLOS NEVES DA CUNHA AREIAS
DOUTOR MANUEL JESUS FALCAO PESTANA VASCONCELOS
DOUTOR JOÃO FRANCISCO MONTENEGRO ANDRADE LIMA BERNARDES
DOUTORA MARIA LEONOR MARTINS SOARES DAVID
DOUTOR RUI MANUEL LOPES NUNES
DOUTOR JOSÉ EDUARDO TORRES ECKENROTH GUIMARÃES
DOUTOR FRANCISCO FERNANDO ROCHA GONÇALVES
DOUTOR JOSE MANUEL PEREIRA DIAS DE CASTRO LOPES
DOUTOR ANTÓNIO ALBINO COELHO MARQUES ABRANTES TEIXEIRA
DOUTOR JOAQUIM ADELINO CORREIA FERREIRA LEITE MOREIRA
DOUTORA RAQUEL ÂNGELA SILVA SOARES LINO

## Professores Jubilados ou Aposentados

ABEL VITORINO TRIGO CABRAL
ALEXANDRE ALBERTO GUERRA SOUSA PINTO
ÁLVARO JERONIMO LEAL MACHADO DE AGUIAR
AMÂNDIO GOMES SAMPAIO TAVARES
ANTONIO AUGUSTO LOPES VAZ
ANTÓNIO CARLOS DE FREITAS RIBEIRO SARAIVA
ANTÓNIO CARVALHO ALMEIDA COIMBRA
ANTÓNIO FERNANDES OLIVEIRA BARBOSA RIBEIRO BRAGA
ANTÓNIO JOSÉ PACHECO PALHA
ANTÓNIO MANUEL SAMPAIO DE ARAÚJO TEIXEIRA
BELMIRO DOS SANTOS PATRICIO
CÂNDIDO ALVES HIPÓLITO REIS
CARLOS RODRIGO MAGALHÃES RAMALHÃO
CASSIANO PENA DE ABREU E LIMA
DANIEL SANTOS PINTO SERRÃO
EDUARDO JORGE CUNHA RODRIGUES PEREIRA
FERNANDO TAVARELA VELOSO
FRANCISCO DE SOUSA LÉ
HENRIQUE JOSÉ FERREIRA GONÇALVES LECOUR DE MENEZES
JORGE MANUEL MERGULHAO CASTRO TAVARES
JOSÉ CARVALHO DE OLIVEIRA
JOSÉ FERNANDO BARROS CASTRO CORREIA
JOSÉ LUÍS MEDINA VIEIRA
JOSÉ MANUEL COSTA MESQUITA GUIMARÃES
LEVI EUGÉNIO RIBEIRO GUERRA
LUÍS ALBERTO MARTINS GOMES DE ALMEIDA
MANUEL ANTÓNIO CALDEIRA PAIS CLEMENTE
MANUEL AUGUSTO CARDOSO DE OLIVEIRA
MANUEL MACHADO RODRIGUES GOMES

MANUEL MARIA PAULA BARBOSA

MARIA DA CONCEIÇÃO FERNANDES MARQUES MAGALHÃES

MARIA ISABEL AMORIM DE AZEVEDO

MÁRIO JOSÉ CERQUEIRA GOMES BRAGA

SERAFIM CORREIA PINTO GUIMARÃES

VALDEMAR MIGUEL BOTELHO DOS SANTOS CARDOSO

WALTER FRIEDRICH ALFRED OSSWALD

## List of original articles

Ao abrigo do Art.º 8º do Decreto-Lei nº388/70 fazem parte desta dissertação as seguintes publicações:

1. Oliveira CM, Pina MF. Spatial distribution and temporal trends of age-standardized incidence hip fracture rates across and over time within Portugal (2000-2010)
2. Oliveira CM, Economou T, Bailey T, Mendonça D, Pina MF. The interactions between municipal socioeconomic status and age on hip fracture risk. Osteoporos Int, 2014, DOI: 10.1007/s00198-014-2869-0, impact factor: 4.039
3. Oliveira CM, Alves S, Pina MF. Marked socioeconomic inequalities in hip fractures incidence rates during the bone and joint decade (2000-2010): age and sex temporal trends in a population-based study
4. Oliveira CM, Economou T, Bailey T, Carvalho M, Pina MF. Climatic effect on spatial-temporal variations of hip Fracture in Portugal (2000-2010)
5. Oliveira CM, Alves S, Teixeira H, Economou T, Bailey T, Pereira-da-Silva J, Pina MF. Regional drinking water composition effects on hip fracture risk. A spatial analysis of nationwide hospital admissions from 2000 to 2010
6. Oliveira CM, Pina MF. Trends in the Hip Arthroplasties: A Population-Based Study in sixteen Countries (1997-2010) from Europe, North and South of America and Oceania.

To my parents, António Carlos and Maria da Graça

To my beloveds Gil and Bárbara

To my brother, sister in law and nephews, Luís, Rosa, Sofia and Pedro

# Acknowledgment

The limited space of this acknowledgment section does not allow me to thank all the people who, throughout my Ph.D. in Public Health, helped me, directly or indirectly, to accomplish my goals and to reach such an important milestone in my academic career. Thus, I leave a few words of profound gratitude.

To Professor Maria de Fátima Pina, I express my deepest appreciation for the orientation and unconditional support that undoubtedly raised my scientific knowledge and encouraged me to always seek for deeper knowledge and always do things better. I also appreciated the opportunity you gave me to integrate your research group, GeoEpidemiology. I acknowledge with gratitude the confidence and the sense of responsibility that you instilled me at every stage of the Ph.D. Thank you for the friendship and good humor that you gave me over this step.

To Professor Denisa Mendonça, I express my sincere appreciation for the co-orientation of this work. Thank you for the total availability, motivation, professionalism, concern and friendship that you have always provided me. I appreciate all the support and vital contribution to get this project done.

To Professor Trevor Bailey, my heartfelt thanks for the co-supervision of this work. I thank all the stimuli and challenges provided for the accomplishment of this thesis. His great wisdom was essential for the success and sense of satisfaction achieved at the end of this work. I am also grateful for the warm welcome in your institution and for giving me the opportunity to "breathe" a different scientific environment, beyond my native institutions, which strongly contributed to my scientific expertise.

To my colleagues and friends from GeoEpidemiology group, who were always present: Sandra Alves, Hugo Teixeira, Alexandre Magalhaes, Ana Isabel Ribeiro, Roseanne Autran, and Andreia Olhero, and to those whom I had the privilege to meet throughout this journey: Sonia Campos, Alaide Santos, Diana Luzio, Sílvia Araújo, Andrea Pires, Marta Guilherme, Lisa Afonso, and Manuela Senra, as well as Theodoros Economou from University of Exeter, my warmest thanks for all your friendship, companionship and help, decisive in achieving this thesis. Thank you for sharing great moments and for supporting me in the difficulties and hard times.

My warmest thanks to the Institute of Biomedical Engineering and the Institute of Public Health of the University of Porto, for having welcomed me in this journey of my Ph.D., and to the Faculty of Medicine of the University of Porto, for having accepted me in this Ph.D. program. I'm very grateful for all the excellent conditions provided during this work, within a high quality and technical demanding environment. Sincere thanks to the University of Exeter, for having welcomed me during three excellent months, where I was able to develop an intensive, productive and of huge scientific relevance work. Finally to all institutions I've attended, at some point during my educational path, the Faculty of Engineering of University of Porto, the Superior Institute of Agronomy of the Technical University of Lisbon and the University of Beira Interior, to all of them my deepest thanks, they were decisive to my academic and scientific background.

To all my dear friends, to my working partners, and to all who directly or indirectly helped me and accompanied me throughout these years, to all of you, thank you very much for all the support and for all the words of encouragement and strength.

## Dedication

I dedicate this work:

To my parents, Antonio Carlos and Maria da Graça, for all the encouragement, unconditional support, and for all the teachings and values that you instilled in me throughout life.

To Gil and Bárbara, for being part of my life and filling my days of meaning; for all the love, encouragement, support and affection they have always shown. My beloveds, please forgive my absences in some moments of this journey.

To my brother, Luís, and my sister in law, Rosa, for the admiration that I feel for you, for your perseverance, for letting me full of pride be your sister and for the wonderful smiles of my nephews, Sofia, and Pedro.

**Content**

# List of Figures

## Subsection 3.1



## Subsection 3.2

## Subsection 3.3



## Subsection 3.4



## Subsection 3.5

## Subsection 3.6

# List of Tables

## Subsection 3.2



## Subsection 3.3

## Subsection 3.4



## Subsection 3.6

# List of Abbreviations

AAC – Annual absolute change, per 100,000 persons-year

ACSS – Central Administration of the National System (Administração Central do Sistema de Saúde)

AgGr – Age Group

AIC – Critério de informação Akaike

AIR – Age-specific incidence rates

Alu – Aluminum, measured by µg/l Pt

ANOVA – Analysis of variance

ARC – Annual relative change (%)

ASIR – Age-standardized incidence rates

ATF – Artroplastia total do fémur

BJD – Bone and joint decade

BJD-Portugal – Bone and joint decade in Portugal

BMD – Bone mineral density

Cad – Cadmium, measured by µg/l Pt

Cal – Calcium, measured by mg/l Pt

CAP – Composição da água potável

CAR – Conditional autoregressive

CF – Climatic factors

CIR – Crude incidence rates

Col – Color grade indicator of organic content in water, measured by mg/l Pt

CrI – Credible interval

DP – Desvio padrão

DRG – Diagnosis Related Groups (Grupos de Diagnósticos Homogéneos)

DWC – Drinking water composition

EB – Empirical Bayes

EBASIR - Empirical Bayes of age-standardized incidence rates

ERSAR – Entidade Reguladora dos Serviços de Águas e Resíduos (Official Institute of Water)

ESE – estatuto socioeconómico

EU – European Union

EU27 – Refers to the 27 countries of the European Union

FC – Factores climáticos

FF – Fracturas do fémur

Flu – Fluoride, measured by mg/l Pt

GAM – Generalized additive model

GINI index - GINI index

GIS – Geographic information system

GLM – Generalized linear model

HF – Hip fractures

HRT – Hormonal replacement treatment

ICD-9-CM – International Classification of Diseases, 9th Revision, Clinical Modification

IGIF – Instituto de Gestão Informática e Financeira da Saúde (Institute of Computer Management and Financial Health)

INE – Instituto Nacional de Estatística

IOF – International Osteoporosis Foundation

IPMAR – Instituto Português do Mar e da Atmosfera (Official Institute of Meteorology)

IQR – Inter-Quartile range

Iron – Iron, measured by µg/l Pt

IU – International Unit

km – Kilometer

Lat – Latitude

Lon – Longitude

Magn – Magnesium, measured by mg/l Pt

Mang – Manganese, measured by µg/l Pt

MCMC – Markov Chain Monte Carlo

mg – milligram

µm – microgram

NFrat – Number of hip fractures

NHDR – National Hospital Discharge Register

NPop – Number of population

NTha - Number of total hip arthroplasties

OCDE – Organisation for Economic Co-operation and Development

PAC – Period absolute change, per 100,000 persons-year

pH – pH (unit of pH)

PRC – Period relative change (%)

PTH – Parathyroid hormone

PY – Persons-year

QoL – Quality of life

Ref – Reference

RR – Relative risk

RurUrb – Rural and urban condition

SD – Standard Deviation

SES – Socioeconomic status

SIG – Sistemas de Informação Geográfica

SMR - Standardized morbidity ratio

SNS – Serviço Nacional de Saúde

THA – Total hip arthroplasty

UK – United Kingdom

USA – United Status

WHO – World Health Organization

# Abstract


**Introduction:** Hip fractures (HF) are one of the major public health problems given the high associated morbidity and mortality, besides the high economic impact of the treatment (e.g. total hip arthroplasties - THA) and recovery. The HF risk seems to be multifactorial and individual factors play an important role in this process, however, the high variability between and within regions (across and over time) suggests that there are possible environmental factors underlying these geographic differences.

**Objectives:** The overall aim is to characterize and understand the spatial and temporal variation of HF in Portugal (2000-2010); analyze how variability in municipality socioeconomic status (SES), climatic factors (CF) and drinking water composition (DWC) might explain part of this spatial-temporal variation; and analyze how the temporal trends (1997-2010) of one of the most commonly used treatments for HF (THA) differs across sixteen countries from Europe, North and South of America and Oceania.

**Methods:** Hip fracture data were obtained from the National Hospital Discharge Register; municipality SES based on a set of variables from Official Institute of Statistics (INE); CF data from Official Institute of Meteorology (IPMAR); DWC data from Official Institute of Water (ERSAR) and THA data from different resources available for each country (e.g. National Hospital Discharge Register, annual reports, among others). Spatial and temporal analysis and geographical information systems (GIS) was used to address the objectives of this thesis. For spatial, temporal and spatial-temporal modeling generalized linear models (GLM), generalized additive models (GAM) and geostatistical models were used and these have been implemented in some cases in a Bayesian framework using Markov Chain Monte Carlo (MCMC) estimation and in others in a frequentist way.

**Results:** A spatial and temporal variation was found in HF with a clear pattern of seasonality. Socioeconomic status might explain part (but not all) of the municipalities variability of HF and CF seems to explain part of the seasonality pattern of HF but not much of spatial and annually variability. Part of remaining variability of HF seems to be explained by DWC. One of the treatments for HF, THA, showed wide differences in temporal trends between countries.

**Conclusions:** The research presented in the current thesis shows that socioeconomic status and the environmental factors might explain part of the spatial and temporal variability on HF; although it seems that there is still some variability unexplained and further investigation is needed to fully understand the spatial and temporal variation in HF risk to help decision-makers to develop more effective treatment and interventions programs.

**Keywords:** Hip; hip fracture; total hip arthroplasties; climatic factors; drinking water composition; spatial, temporal and spatial-temporal analysis

# Resumo


**Introdução**: As fracturas do fémur (FF) são um grande problema de saúde pública dada a sua alta morbilidade e mortalidade bem como o alto impacto económico do tratamento requerido (por exemplo, artroplastia total do fémur - ATF) e da sua recuperação. O risco de FF parece ser multifactorial e os factores individuais desempenham um papel importante neste processo, no entanto, a enorme variabilidade existente entre e dentro das regiões (quer seja transversal ou ao longo do tempo) sugerem que existem possíveis factores ambientais subjacentes a estas diferenças geográficas.

**Objectivos**: O objectivo global é caracterizar e compreender a variação espacial e temporal das FF em Portugal (2000-2010); analisar como a variabilidade municipal do estatuto socioeconómico (ESE), dos factores climáticos (FC) e da composição da água potável (CAP) pode explicar parte desta variabilidade espaço-temporal; e analisar como as tendências temporais (1997-2010) de um dos tratamentos mais usados para as FF (ATF) difere entre dezasseis países da Europa, Norte e Sul da América e Oceânia.

**Métodos**: Os dados das fracturas do fémur foram obtidos do Registo Nacional de Internamentos Hospitalares, do ESE do município foi obtido através de um conjunto de variáveis recolhidas pelo Instituto Português de Estatística (INE), os dados dos FC do Instituto Português do Mar e da Atmosfera (IPMAR), os dados da CAP da Entidade Reguladora dos Serviços de Águas e Resíduos (ERSAR) e os dados das artroplastias totais a partir de diversas fontes disponíveis para cada país (por exemplo, registo nacional de internamentos hospitalares, relatórios anuais, entre outros). Análise espacial e temporal e sistemas de informação geográfica (SIG) foram usados para responder aos objectivos desta tese. Para a modelagem espacial, temporal e espaço-temporal foram usados modelos lineares generalizados (GLM), modelos aditivos generalizados (GAM) e modelos geoestatísticos, estes foram implementadas nalguns casos, em ambiente de estimação Bayesiano usando Cadeias de Markov Monte Carlo (MCMC) e noutros de forma frequentista.

**Resultados**: Uma variação espacial e temporal foi observada no risco de FF com um claro padrão de sazonalidade. O ESE parece explicar parte, mas não toda, a variabilidade das FF entre os municípios e os FC parecem não explicar grande parte da variabilidade espacial e bem como da tendência anual mas parece explicar parte do padrão sazonal. Parte da variabilidade que fica por explicar parece ser parcialmente explicada pela CAP. Um dos tratamentos utilizado para FF, ATF, mostrou grandes diferenças nas tendências temporais entre países.

**Conclusões**: A investigação desenvolvida na corrente tese evidência que factores socioeconómicos e ambientais podem explicar parte da variabilidade espacial e temporal no risco de FF; no entanto alguma variabilidade fica ainda por explicar e futuras investigações serão necessárias para explicar tal variação, de forma a ajudar os decisores políticos a desenvolverem programas de tratamento e intervenções mais eficazes.

**Palavras-chave**: Fémur; fractura do fémur; artroplastia total do fémur; factores climáticos; composição de água potável; análise espacial, temporal e espaço-temporal

# Chapter 1. Introduction

## 1.1 State of art

Hip fractures (HF) are one of the major causes of loss disability for people 50+ years old worldwide [1], especially in women. The HF incidence rates increase exponentially with age in both women and men and 90% of the HF affects individuals 50+ years old [2]. Hip fractures are more frequent in women than in men: one in three women and one in five men will have a fracture in individuals 50+ years old [3]. Among all fractures, the hip fractures are those with most severe consequences in terms of live lost and in terms of negative impact on quality of life (QoL) [4] besides the high direct and indirect costs associated with treatment and recovery that represent to the health care systems [5]. Hip fracture has been recognized as a serious consequence of osteoporosis [4] which is a disease characterized by reduced bone mass and disruption of bone architecture [3]. Osteoporosis is responsibility for 8.9 million fractures annually worldwide and about one-third is in European countries [3]. Osteoporosis and falls are the main cause of HF [6]. Ninety percent of HF results from low energy falls [7] and the outcome is dramatic: fatality after one year was 34.6% for men and 21.4% for women in a longitudinal study [8]; and among independent women before the fracture, half of them need help in daily activities after a year of the event [9]. One-third of older individuals will fall annually; of this 5% will have a fracture and 1% will have an HF [10].

Studies have shown geographic variation between and within countries on HF incidence [4, 11, 12]. Scandinavian countries and North America present a higher incidence of HF rates and Southern European countries present seven-fold lower rates [13], although HF are lower in Latin American countries [4]. Also, a great heterogeneity has been reported within country and Portugal is one of this cases. Portugal has a large variability within the country, where some regions have HF rates 3 times higher than others [14]. Reasons for this geographic variation are unknown. Genetic and environmental factors might play an important role in this process since interfere in its etiology. However, Portugal is not a country with a strong genetic heterogeneous as some others countries and environmental factors are more plausible to justify the underline of such variability. Other possible explanation might be differences in regional socioeconomic status since they are related to levels of physical activity and nutrition quality [3]. Regions with a high level of social deprivation, a high percentage of individuals with poor diet, insufficient physical activity, deficient access to the health care and to preventive actions may present a higher risk of osteoporosis and HF [15].

The absolute number of HF is increasing in almost all countries due to the increase in life expectancy [16, 17]. Secular trends of increasing age-standardized HF incidence rates have been reported in the past [4], over the last two decades there are reports showing declines in these rates, although they are scarce and the reason for such unknown pattern. A decreasing trend over the last decade has been reported in Scandinavia countries such as in Denmark [18], Sweden [19], Finland [20] Norway [21], and also in France [22], Spain [23], Switzerland [24] and Netherlands [25] and more recently, in Austria [26] and Greece [27]. In Portugal, a decreased trend in the HF was observed after 2003 for women [28]. In Germany, stabilization or decreases were shown within age and sex subgroups [29]. Differences in the temporal trends were also described between and within countries with different patterns by sex and age groups [16, 28] and this might be the results of cohort or period effects reflecting important changes in population such as improved nutrition and better maternal health; improved prevention strategies against osteoporosis, both medical (pharmaceutical treatment) and non-medical (prevention of falls) in recent years [28, 30, 31]; changes in political and economic regime that might affect health of population or access to health [32]; among others. In Portugal, surprising results showed fluctuations in risk of HF, coincident with all the major political and economic changes in the first half of the 20th century in Portugal [32] and the abrut decreasing observed after 2003 are coincident with the abrupt increase in bisfosfanate sales [28].

Changes in temporal trends have been accompanied by seasonal patterns with higher incidence rates in winter [33]. The underline reason for such seasonal variation are not well understood, although might be caused by meteorological factors that can have some impact on the bone metabolism and muscle strength. During winter, the low sun exposition may decrease the synthesis of vitamin D, with a direct effect on muscle strength and balance [34] and on the calcium and skeletal homeostasis [35]. Low temperatures may also, indirectly, contribute to the increase of bone loss, muscle weakness and bone fragility, because they are associated with low levels of physical activity [36, 37]. Moreover, there is an increased risk of falls in winter due to adverse weather conditions, poor visual acuity [33] and impairment of movement caused by an excess of clothes. Latitude and seasonal variation have been described as a possible explanation for the highest HF incidence in Scandinavia countries [33]. Also meteorological factors might have some influence on the spatial distribution of HF and even might explain some particular anomaly in time and space in the HF risk – probably some high incidence in a particularly regions and/or time might be a consequence of weather conditions that might increase the susceptible to fall or might promote less activity and less synthesizes of vitamin D due to more adverse weather conditions.

Others environmental factors that can explain part of the spatial variability of HF might be drinking water composition, since it is known that high or/and long exposure to low levels of heavy metals or mineral might promote deterioration or might be beneficial for bone quality [38]. However, little is known about the relation between drinking water exposure and bone heath. The quality of municipality drinking water might differ and the variability of the amounts of mineral such as calcium, magnesium, iron, fluoridate, among others in drinking water might be one of the possible explanation for the spatial pattern [39-43].

Hip fractures are usually associated with substantial pain, suffering and disability for those affected [3]. The majority of hip fractures are treated operatively with surgical techniques that will depend on the type of fracture. Fifty percent of all HF are at the femoral neck and the three major surgical procedures for this type of fracture are *in situ* fixation, partial-arthroplasty and total arthroplasty [44]. These procedures are associated with higher cost [45], and the social disparity has been reported with lower rates for those in deprived socioeconomic status [46-48]. To establish and implement equitable public health policies it is important to understand the disparities among populations, including disparities between countries; especially in this period of financial constraints. Over time, an increase in total hip arthroplasties (THA) has been described in almost developed countries [49-52], although the rates across countries and the velocity of changes over time greatly vary among countries [53, 54]. Understanding the trends variability in the arthroplasties is important to better address the cultural and the socioeconomic factors underlying these trends.

It is important to clarify and identify factors responsible for this across and over time heterogeneity of HF risk (and of its prevention and/or treatment) between and within countries and understand its reversibility. The social and economic burden of hip fractures reinforces the importance of more epidemiological studies to understand the spatial and temporal patterns of HF risk and to identify populations at higher risk to help decision-makers to develop more effective treatment and interventions programs.

## 1.2 Research Objectives

The main objective of this Ph.D. Project is to characterize and understand the spatial and temporal patterns in the incidence of hip fractures among patients above 50 years old during the Bone and Joint Decade (2000-2010) in Portugal and to identify risk factors that may explain such patterns.

Specific objective are:

1. To describe the spatial distribution and temporal trends of age-standardized incidence hip fracture rates across and over time within Portugal (2000-2010)
2. To analyze and quantify the relationship between hip fracture and socioeconomic status as well as the relevance of the interaction between age and SES on HF risk, in Portugal (2000-2010).
3. To investigate the temporal trends of hip fracture incidence rates during the Bone and Joint Decade (2000-2010), by sex and age group according to municipality SES cluster.
4. To analyze and quantify the climate factors effects on the spatial-temporal distribution of hip fracture, at municipality level in Portugal from 2000 to 2010.
5. To analyze the regional drinking water composition effects on hip fracture risk. A spatial analysis of nationwide hospital admissions from 2000 to 2010
6. To describe the temporal trends of total hip arthroplasty incidence rates, from 1997 to 2010, among individuals with more than 45-year-old, in different countries from Europe, North and South of America and Oceania and to provide projections between 2010 and 2015.

## 1.3 Thesis outline

This thesis is divided into four chapters. This chapter 1 comprises the state of the art and the objectives of this thesis. The chapter 2 performs an overview of material and methods used; chapter 3 the articles prepared for publication, and chapter 4 covers the discussion and the conclusion of all relevant results of this thesis.

Chapter 3 includes six sections with specific proposes summarizes bellow:

Subsection 3.1 refers to a descriptive study that explores and discusses the spatial and temporal trends of hip fracture. In this subsection, we want to characterize the temporal and the spatial distribution of hip fracture in Portugal and positioned Portugal in the context of international studies on this topic.

Subsection 3.2 comprise a cross-sectional ecological study that aims to explain if the possible spatial variation of HF observed in previous subsection 3.1 can be explained by differences in the municipality socioeconomic position.

Subsection 3.3 reports a longitudinal ecological study that adds information to the cross-sectional study presented in subsection 3.2. In this subsection, we analyze if there are some different pattern in the temporal trend by municipality socioeconomic position. We want to explore if regions that are at a better position in term of socioeconomic position can be better to adapt over time to the recent economic recession observed in Portugal.

Subsection 3.4 presents the spatial-temporal ecological study that aims to explain if the remain spatial variation of hip fracture that cannot be explained by municipality socioeconomic position (if there is any) can be explained by municipality climatic factor variation such as temperature, precipitation, sun duration, among other. Also, if the temporal trends (annual variation and seasonality pattern) might be explained by the differences in these climatic factors over time.

Subsection 3.5 reports a spatial ecological study having as objective to explain if the remain spatial variation of hip fracture that cannot be explained by municipality socioeconomic position (if there is any) can be explained by drinking water composition variation such as calcium, magnesium, fluoride, iron, aluminum, among others.

Subsection 3.6 presents an ecological study involving different countries to characterize the differences in temporal trends of total hip arthroplasties.

# Chapter 2. Materials and Methods

## 2.1 Data sources

### Hip fracture data

Hip fracture (HF) data were obtained from National Hospital Discharge Register (NHDR). Each record in the NHDR corresponds to one discharge and contains patients information such as: sex, age, first cause of admission and main diagnosis (and up to 19 secondary causes and 19 secondary diagnoses), coded according to the International Classification of Diseases, version 9, Clinical Modification (ICD9-CM), municipality of patient's residence, date of admission and discharge, hospital to and hospital from whenever there is a transfer between hospitals, among others [55]. It was selected all hospital admissions, from 1 January 2000 to 31 December 2010, of patients aged 50 years and over with a discharge diagnosis of HF (ICD9-CM codes 820.x) caused by traumas of low/moderate energy (ICD9-CM codes E849.0, E849.7 and E880-E888). We excluded readmissions (ICD9-CM codes 996.4 and V54.x) and pathological fractures (ICD9-CM codes 170.x and 171.x). For different purposes, as described in following sections, the number of HF was aggregate by (1) Sex, age group and year; (2) Sex, age group, year, and month; (3) Sex, age group, municipality and year; and (4) Sex, age group, municipality socioeconomic status, and year.

### Total hip arthroplasties data

Total hip arthroplasties data (THA), between 1997 and 2010, were provided from different resources for sixteen countries: Nationwide Inpatient Sample for United State of America (USA); Hospital Morbidity Database for Canada; Registro de Altas – CMB for Spain; National Hospital Discharge Register (NHDR) for Portugal, Netherlands, Australia, Germany and Finland; National Hospital Database for France; Hospital Discharge Records Database for Italy; Hospital Statistical FSO for Switzerland; Database SUS (Sistema Único de Saúde) for Brazil; and annual reports of each country for Denmark, England and Wales, New Zealand and Slovakia. The number of THA was aggregated by sex, age group, country, and year.

**Demographic and socioeconomic data**

Demographic and socioeconomic data for Portugal were provided from National Institute of Statistics (Instituto Nacional de Estatística – INE). For different purposes, as described below sections and whenever possible, data (e.g. number of population) were aggregated by (1) Sex, age group and year; (2) Sex, age group, year, and month; (3) Sex, age group, municipality and year; and (4) Sex, age group, municipality socioeconomic status and year.

Demographic data for others countries were provided by EUROSTAT or by the official National Institute of Statistics and whenever possible were aggregated by Sex, age group, country, and year.

**Meteorological data**

Climatic factors (CF) data were obtained from the National Institute of Meteorology ("Instituto Português do Mar e da Atmosfera" – IPMAR) and contain daily information on mean temperature (ºC), precipitation (mm), relative humidity (%), daily amount of sunshine (hours) and atmospheric pressure (hPa) from 18 meteorological station from the 18 districts of Continental Portugal. Data were aggregated by the station, month and year and mean values were used.

**Drinking water composition data**

Data from physical and chemical parameters of municipality drinking water composition (DWC) were obtained from the official institute of quality water "Entidade Reguladora dos Serviços de Água e Resíduos" (ERSAR) and contain information such as aluminum, cadmium, calcium, color, fluoride, iron, magnesium, manganese and pH. Data was aggregated by median sampling for each municipality and year (when available).

**Derived data**

The Age-specific Incidences Rates (AIR) and Age-Standardized Incidence Rates (ASIR) of HF expressed as admissions per 100,000 persons-years (PY) were computed. The ASIR was directly standardized with respect to 2006 European population to control the differences that may occur due to demographic change in the population age structure.

The age-standardized incidence rates (ASIRs) expressed as admissions per 100,000 PY and the standardized morbidity rates (SMR) of THA were estimated using the indirect methods of standardization and taking the USA age structure population in 1997 as a reference to control for differences that may occur due to demographic change in the population age-structure per country.

## 2.2 Statistical analysis

The statistical analyses performed in each study are described in each article. An overview of these methodologies and the reasons for their use are explained briefly here.

To explore the spatial pattern of age-standardized incidence rates of HF across the municipality, the global and local Moran index was used to identify spatial clusters. To explore the temporal trend of age-standardized across municipalities, generalized linear models (GLM) were used assuming a Gaussian distribution for response variable and the Moran index was applied to the slope of such models to identify a cluster of increase or decrease age-standardized across the municipality.

To analyse the effect of socioeconomic status (SES) of the residence area on the HF risk as a possible explanation for the spatial variability on HF risk; as well as, to analyse the effect of the interaction between age group and SES on the risk of hip fracture, a spatial Bayesian hierarchical regression model was used to assess the relationship between mean HF rates and SES. Age and rural conditions were included in the model as predictors to allow for the (possible) different behavior of HF rates between various categories of age and rural conditions. An interaction term between age and SES was also included to capture the possible modifiable effect of age in the relation between SES and HF incidence. The model included two random effects at the municipality level. One of the random effects accounted for the unexplained heterogeneity in HF rate due to unobserved municipality-level factors while the other allowed for spatially structured dependence in measurements of HF in municipalities that were spatially close. The latter relates to the fact that HF incidence in two nearby municipalities tends to be more similar (in terms of risk) than in two areas randomly chosen. The model described above was implemented in a Bayesian framework and estimated using Markov Chain Monte Carlo (MCMC). In this framework, parameters are treated as random variables whose "prior" distribution expresses the uncertainty about their value before any data is observed.

To explore the annual temporal trend of age-specific incidence rates (AIR) of HF (2000-2010) across regional SES, generalized additive models (GAM) were used to identify shape and points where the temporal trend of AIR changed significantly in magnitude and/or direction during the study period. It was assumed that response variable followed a Poisson distribution and a log link function were used in GAM modeling. In the case where overdispersion (excess variation with respect to a Poisson model) was observed, a negative binomial distribution was considered. These models allow great flexibility as they can incorporate non-parametric functions, such as spline functions (smoothers, useful in revealing possible nonlinearities in the effect of the predictors), to take into account possible non-linearity relationship between explanatory and response variables.

To interpolate meteorological data station to a minimum grid that contains Portugal and predicts for each centroid of the municipality (where no measurements were available), a geostatistical procedure was used. It was assumed an isotropic spatial process for each climatic factor (CF) and a suitable empirical semivariogram model was selected to estimate the theoretical semivariogram which describes the spatial dependence among the data at each station. Using the estimated semivariogram model, a predictive technique (Kriging) was utilized to predict the CF values at specific spatial points relating to each municipality. Predictive technique Kriging is more suitable in cases where spatial data had unidentified neighbourhoods.

To analyse the effect of climatic factors (CF) on the HF risk as a possible explanation for the spatial and temporal variability on HF risk; a negative binomial generalized additive model (GAM) was used to estimate the relative risk (RR) of HF associated with variations in CF along with 95% confidence intervals (CIs) for inference. The possible confounders age-group, socioeconomic status, and rural conditions were included into the model to allow (possible) different behavior of HF between various categories of age, socioeconomic status and rural conditions. In addition, the centroid of each municipality, the month and year of HF occurrence were also included into the model to account for possible spatial, seasonality and annually temporal trends in HF risk.

To analyse the effect of drinking water composition (DWC) on the HF risk as a possible explanation for the spatial variability on HF risk; a spatial negative binomial generalized additive model was used to estimate the relative risk (RR) of HF associated with variation in DWC along with 95% confidence intervals (CIs). The possible confounder's age-group, socioeconomic status, and rural conditions were included into the model to allow (possible) different behavior of HF between the various categories. In addition, the centroid of each municipality, the year, and month of HF occurrence were also included into the model to account for possible spatial, seasonality and temporal trends in HF risk.

To explore the annual trend of the age-standardized incidence rates of total hip arthroplasties (THA) by country (1997-2010), a general additive model (GAM) was used to inspect and identify shape and points where the trend changes significantly in magnitude and direction and to interpolate and extrapolate the estimated values where no measurements were available. It was assumed that response variable, the number of THA, is distributed as a Poisson distribution random variable or is distributed as a negative binomial random variable in the case where overdispersion (excess variation with respect to a Poisson model) was observed.

# Chapter 3. Results

## 3.1 Spatial distribution and temporal trends of age-standardized incidence hip fracture rates across and over time within Portugal (2000-2010)

# SPATIAL DISTRIBUTION AND TEMPORAL TRENDS OF AGE-STANDARDIZED INCIDENCE RATES OF HIP FRACTURE ACROSS AND OVER TIME WITHIN PORTUGAL (2000-2010)

**Oliveira CM, Pina MF**

**Carla Maria Oliveira**

i3S - Instituto de Investigação e Inovação em Saúde, Universidade do Porto, Portugal;

INEB - Instituto de Engenharia Biomédica, Universidade do Porto, Rua do Campo Alegre, 823, 4150-180 Porto, Portugal;

ESTSP/IPP - Escola Superior de Tecnologia da Saúde do Porto, Instituto Politécnico do Porto, Rua Valente Perfeito, 322, 4400-330 Vila Nova de Gaia, Portugal;

FMUP - Departamento de Epidemiologia Clínica, Medicina Preditiva e Saúde Pública da Faculdade de Medicina da Universidade do Porto, Al. Prof. Hernâni Monteiro, 4200 - 319 Porto, Portugal

ISPUP - Instituto de Saúde Pública da Universidade do Porto, Rua das Taipas 135, 4050-600, Porto, Portugal

coliveir@ineb.up.pt

**Maria Fátima Pina**

ICICT/FIOCRUZ - Instituto de Comunicação e Informação em Saúde/ Fundação Oswaldo Cruz, Av. Brasil, 4365 - Pavilhão Haity Moussatché - Manguinhos, Rio de Janeiro, CEP: 21040-900,

i3S - Instituto de Investigação e Inovação em Saúde, Universidade do Porto, Portugal;

INEB - Instituto de Engenharia Biomédica, Universidade do Porto, Rua do Campo Alegre, 823, 4150-180 Porto, Portugal;

FMUP - Faculdade de Medicina da Universidade do Porto, Al. Prof. Hernâni Monteiro, 4200 - 319 Porto, Portugal

CARTO-FEN/UERJ - Departamento de Engenharia Cartográfica, Faculdade de Engenharia da Universidade do Estado do Rio de Janeiro. Rua São Francisco Xavier, 524/4ºandar, Maracanã, CEP:20550-900, Rio de Janeiro – RJ, Brazil.

fatima.pina@icict.fiocruz.br

**Corresponding author**: C M Oliveira; coliveira@ineb.up.pt; phone: +351 226074900 ; Fax: +351 226094567; INEB, Instituto de Engenharia Biomédica, Universidade do Porto, Rua do Campo Alegre, 823, 4150-180 Porto, Portugal

**Acknowledgments**: The work was financed by Portuguese funds through FCT – Fundação para a Ciência e a Tecnologia in the framework of project UID/BIM/04293/2013. Authors would also like to thank FCT for the grant PTDC/SAU-EPI/113424/2009.

We acknowledge the Central Administration of Health Services (ACSS) for the data from the National Hospital Discharge Register.

**Conflict of Interest**: Carla Maria Oliveira and Maria Fátima Pina declare that they have no conflict of interest.

**Role of funding source**: The funder Fundação para a Ciência e Tecnologia - FCT has no role in this paper.

## ABSTRACT

**Background**: Differences across and over time within countries has been reported. The aim of this work is to analyze the spatial distribution and temporal trends of age-standardized hip fracture (HF) incidence rates across and over time within Continental Portugal from 2000 to 2010.

**Methods**: From the Portuguese Hospital Discharge Database we selected hospitalizations (2000-2010) of patients aged 50+, with HF diagnosis (codes 820.x, ICD9.CM), caused by traumas of low/moderate energy, excluding bone cancer cases and readmissions for after-care. The global and local Moran index was used to identify spatial clusters of age-standardized incidence rates of HF across the municipality. Generalized linear models (GLM) were used assuming a Gaussian distribution for response variable and the Moran index was applied to the slope of such models to identify a cluster of increase or decrease of age-standardized over time across the municipality.

**Results**: We selected 96,905 HF (77.3% in women). Mean age at admission was 81.2±8.5 and 78.2±10.1 years-old ($p<0.001$), women and men respectively. The global Moran index was highly significant for ASIR in 2000 (women: I=0.658, men: I=0.531) and in 2010 (women: I=0.664, men: I=0.672) and for the slope between 2000 and 2010 (women: I=0.538, men: I=0.530); indicating that neighboring districts had closer ASIR and slopes than distant ones. Women present a decrease in age-standardized incidence rates in almost all municipalities, except for inland municipalities, while men present an increase in almost all municipalities, especially for inland municipalities.

**Conclusions**: Differences across and over time in age-standardized hip fracture incidence rates within Continental Portugal were found in our study, although this is an exploratory analysis and the underlying reasons for such high variability need further investigation.


**Keywords**: Hip fracture, geographic distribution across and over time, Moran index, generalized linear models

**Introduction**

Several studies have reported a large heterogeneity between countries in the incidence of hip fractures (HF), being more prevalent by 10-fold in some countries over others [1]. Countries with the highest rates include Denmark, Sweden and Norway and those with the lowest rates include Nigeria, South Africa and Ecuador for both sexes [1, 2]. Variation within countries has also been reported [3, 4]; Portugal presents a 3-fold higher variation incidence between municipalities [4]. Heterogeneity between municipalities has also been reported within homogenous subgroups of populations, such as within sexes and age groups [5]. Differences in regional socioeconomic status, in urbanization, and environmental factors have been pointed out as possible explanations for this spatial variability [6, 7].

Not only have differences across regions been reported, but also differences over time have been described. In countries like the United States (USA), Canada, Northern Europe, Oceania, Hong Kong and Taiwan, an increase followed by a decreasing trend has been described, although in different time points; starting first in the United Kingdom (UK) in the late 1970s, followed by North America in the mid-1980s, Norway and Sweden in the early 1990s and Denmark and Finland in the late 1990s. However, a continuous rising trend has been reported in regions such as Southern Europe, South America and Asia [1, 8]. Differences in changes over time have also been found within homogeneous subgroups of populations, such as sex and age groups [9, 10]. Scandinavian countries present the highest HF incidence; however, a decreasing trend has been observed in the last decade; Finland (1997-2010), Norway (1999-2008) and Sweden (1996-2002) have presented a decrease in age-standardized rates being higher in women than in men (Finland: 1.9% vs. 1%/year, Norway: 1.2% vs. 0.7%/year, Sweden: 1.4% vs. 0.7%/year). In Portugal, a significant decreasing trend was observed between 2003 and 2008 in women but not in men [11]. Germany presents decreased incidence rates for women below 74 years and an increase in women above 75 years of age [12]. Not only have national studies reported differences in trends between countries, there have also been differences in trends between areas within countries. Regional differences in trend between East and West Germany with a higher increase in the East between 1995 and 2004 was observed and one possible explanation for this regional difference in trend might be the contrast in lifestyles such as nutrition, activity levels and environmental factors that were observed before the re-unification [12]. It seems that most of the patterns in temporal trend are in line with the process of development and the stabilization of this process might reflect a stabilization in the HF increase [8]. The underlying mechanisms of the effect of development is unknown; however, this might be a reflection of changes in lifestyle, such as decreased physical activity, alcohol consumption, smoking, bad nutrition (low calcium intake), obesity, and changes in territorial occupation and in environmental conditions due to the process of urbanization, such as water and soil contamination [8]. The recent stabilization and decrease might be due to improved screening and treatment programs, healthier aging, and changes in individual behavior, which has been of growing concern in developing countries more recently [13].

The objective is to analyze the spatial distribution and temporal trends of age-standardized hip fracture (HF) incidence rates in Continental Portugal by the municipality from 2000 to 2010.

## Material and Methods

### Data

We used data from the National Hospital Discharge Register (NHDR), which has been mandatory for all Portuguese public hospitals since 1997. Each record in the NHDR corresponds to one discharge and contains information such as: sex; age; first cause of admission and main diagnosis (and up to 19 secondary causes and 19 secondary diagnoses), coded according to the International Classification of Diseases, version 9, Clinical Modification (ICD9-CM); municipality of patient’s residence; date of admission and discharge, hospital-to and hospital-from whenever there is a transfer between hospitals, among others [14].

We selected all hospital admissions, from 1 January 2000 to 31 December 2010, of patients aged 50 years and over, with a discharge diagnosis of HF (ICD9-CM codes 820.x) caused by traumas of low/moderate energy (ICD9-CM codes E849.0, E849.7 and E880-E888). We excluded readmissions (ICD9-CM codes 996.4 and V54.x) and pathological fractures (ICD9-CM codes 170.x and 171.x). No such data was available for the two autonomous regions, the archipelagos of the Azores and Madeira, and therefore, they were not included in the study (representing 5% of the Portuguese population) (Figure 1). Counts of HF were stratified by the municipality of the patient's residence, admission year, sex and 5-year age groups (50-54… 80-84, 85+).

To calculate the population at-risk or person-years we aggregated data per municipality, sex and 5-year age groups using population data from the 2001 Census and annual official estimates for the other years [15]. The standard population, the 2006 European population, was provided by EUROSTAT and stratified by the 5-year ages used in HF [16].

**Statistical analysis**

We calculated the annual time series of the age-standardized incidence rates of HF (ASIR) expressed as admissions per 100,000 person-years (PY) stratified by sex and municipality between 2000 and 2010. Considering that $\mathrm{NFrat}_{\mathrm{ijts}}$ represents the number of cases in a specific age group i (i = $1, \ldots, 8$), region j (j = $1, \ldots, 278$), year $t$ (j = $2000, \ldots, 2010$) and sex $s$ (s= 1,2) and $\mathrm{NPop}_{\mathrm{ijts}}$ represents the number of population at risk in age group i, region j, year $t$ and sex $s$. The Crude Incidence Rates (CIRs) in each region j, year $t$ and sex $s$ were estimated by $\mathrm{CIR}_{\mathrm{jts}} = \sum_{\mathrm{i}}^{\mathrm{m}} \mathrm{NFrat}_{\mathrm{ijts}} / \sum_{\mathrm{i}}^{\mathrm{m}} \mathrm{Pop}_{\mathrm{ijts}}$ and to control for differences that may occur due to demographic change in the population age structure within each country. The age-standardized rates (ASIRs) in each region j, year $t$ and sex $s$ were estimated using the direct method of standardization:

$$ASIR_{jts} = \frac{1}{\sum_i^m NStPop_i} \times e_{jts}$$

where $\mathrm{NStPop}_{\mathrm{i}}$ represents the number of standard population in age group i, $\mathrm{e}_{\mathrm{jts}} = \sum_{\mathrm{i}}^{\mathrm{m}} \left(\mathrm{NStPop}_{\mathrm{i}} \times \mathrm{CIR}_{\mathrm{ijts}}\right)$ represents the expected number of cases in each region j, year $t$ and sex $s$ if the age structure population is the same as the reference population, and $\mathrm{CIR}_{\mathrm{ijts}} = \mathrm{NFrat}_{\mathrm{ijts}} / \mathrm{Pop}_{\mathrm{ijts}}$ represents the age-specific incidence rate in each age group i, region j, year $t$ and sex $s$.

Rates based on population count are estimates subject to error that can be substantial when the measures have a small number of events in the numerator [17], typically a problem with small geographic areas (e.g. municipalities). Taking into account possible instability in rates due to small numbers in the municipality, an empirical Bayes (EB) approach was used to smooth the local risk [18]. This approach smoothed the incidence rate in a specific region, taking into account a weighting average incidence rate of the neighboring areas depending on the size of the population and the variability of the incidence rate. Then, under the Bayes framework, the locally empirical Bayes estimator for ASIR ($\mathrm{EBASIR_{jts}}$) of HF in each region j, year $t$ and sex $s$ are a combination of the local "average" ASIR of neighbors, $\mathrm{ASIR_{jts}^{ng}}$, and its "variance" $\mathrm{v_{jts}}$ with the observed ASIR, $\mathrm{ASIR_{jts}}$ [19].

$$\mathrm{EBASIR_{jts}} = \theta_{\mathrm{jts}}\mathrm{ASIR_{jts}} + (1 - \theta_{\mathrm{jts}})\mathrm{ASIR_{jts}^{ng}}$$

where:

$$\theta_{\mathrm{jts}} = \frac{\mathrm{v_{jts}}}{\mathrm{v_{jts}} + \frac{\mathrm{ASIR_{jts}^{ng}}}{\mathrm{NPop_{jts}}}}$$

$$\mathrm{v_{jts}} = \frac{\sum_{\mathrm{k \in A_j}} \mathrm{NPop_{kts}}\left(\mathrm{ASIR_{kts}} - \mathrm{ASIR_{kts}^{ng}}\right)^2}{\mathrm{NPop_{jts}^{ng}}} - \frac{\mathrm{ASIR_{jts}^{ng}}}{\overline{\mathrm{NPop_{jts}^{ng}}}}$$

where $\theta_{\mathrm{jts}}$ represents the weight (shrinkage factor); $\mathrm{v_{jts}}$ represents the "variance" of the observed rates around the mean; and $\mathrm{NPop_{jts}}$ represents the number of population in each region j, year $t$ and sex $s$. $\mathrm{A_j}$ represents the subset of the regions that are neighborhoods and $\mathrm{n_j^{ng}} = \#\mathrm{A_j}$ represents the number of neighborhoods to the region j (excluding region j). $\mathrm{NPop_{jts}^{ng}} = \sum_{\mathrm{k \in A_j}} \mathrm{NPop_{kts}}$ represents the number of population of neighborhoods and; $\overline{\mathrm{NPop_{jts}^{ng}}} = \frac{\mathrm{NPop_{jts}^{ng}}}{\mathrm{n_j^{ng}}}$ represents the mean population of neighborhoods of the region j, year $t$ and sex $s$. $\mathrm{ASIR_{jts}}$ represents the age-standardized incidence rates in the region j, year $t$ and sex $s$; and $\mathrm{ASIR_{jts}^{ng}}$ represents the age-standardized incidence rates for the neighborhoods of region j, year $t$ and sex $s$. The $ASIR_{jts}^{ng}$ calculation is based on:

$$\mathrm{ASIR}_{\mathrm{jts}}^{\mathrm{ng}} = \frac{1}{\sum_{\mathrm{i}}^{\mathrm{m}} \mathrm{NStPop_i}} \times \mathrm{e}_{\mathrm{jts}}^{\mathrm{ng}}$$

where $\mathrm{e}_{\mathrm{jts}}^{\mathrm{ng}} = \sum_{\mathrm{i}}^{\mathrm{m}} \left(\mathrm{NStPop_i} \times \mathrm{CIR}_{\mathrm{ijts}}^{\mathrm{ng}}\right)$ represents the expected number of cases for the neighborhoods if the age structure population is the same as the reference population; and $\mathrm{CIR}_{\mathrm{ijts}}^{\mathrm{ng}} = \sum_{\mathrm{k} \in \mathrm{A_j}} \mathrm{NFrat_{ikts}} / \sum_{\mathrm{k} \in \mathrm{A_j}} \mathrm{NPop_{ikts}}$ represents the age-specific incidence rate for the neighborhoods of region j, year $t$ and sex s. For convention, if $\nu_{\mathrm{jts}} < 0$ then $\nu_{\mathrm{jts}} = 0$, which means that $\theta_{\mathrm{jts}} = 0$ and $\mathrm{EBR_{jts}} = \mathrm{ASIR}_{\mathrm{jts}}^{\mathrm{ng}}$. The $\theta_{\mathrm{jts}}$ range between 0 and 1, and depend on the size of the population and variance $\nu_{\mathrm{jts}}$, approaching 1 in areas with large population and 0 in areas with less population [1]. The neighborhood criterion used was the one that shared at least one common border (adjacent regions) – the rook criterion.

After applying the EB approach in municipality ASIR (EBASIR) of HF for all years between 2000 and 2010 and sex, a generalized linear model (GLM) was performed to estimate the temporal trend of EBASIR for all municipalities. We assumed that the EBASIR ($EBASIR_t$) in a specific year ($t = 2000, \ldots, 2010$) and sex follows a Gaussian distribution with mean $\mu_t$ and standard deviation $\sigma$. For each sex and municipality, the parameters of interest of EBASIR were estimated by the following model:

$$EBASIR_t \sim N(\mu_t, \sigma)$$

$$log(\mu_t) = \beta_0 + \beta_1 Year^{(t)}$$

where the fixed effect $\beta_0$ and $\beta_1$ are the intercept and the slope, respectively. $\beta_0$ represent the estimate for EBASIR in 2000 ($EBASIR_{2000} \approx \beta_0$), $\beta_1$ represent the increase in EBASIR per an increase in one unit in time and, consequently, $\beta_0 + \beta_1 \times t$ represent the estimate for EBASIR in year $t$ ($EBASIR_t \approx \beta_0 + \beta_1 \times t$). The annual EBASIR changes were quantified between 2000 and 2010 under the assumption of a constant rate of change for each municipality.

To verify the existence of spatial dependence between municipalities on estimates of $EBASIR_t$, a measure of spatial autocorrelation – the Moran Index – was applied for each year and sex. Global and Local Moran Index was performed. The former is one statistic to summarize the pattern in the whole study area (e.g. clustering, homogeneity) and the latter is local specific statistics – local indicators of spatial autocorrelation (LISA) – to summarize local patterns (e.g. clusters/hot-spots, heterogeneity). The global Moran Index is given by:

$$I = \frac{n \sum_{j=1}^{n} \sum_{i=1}^{n} w_{ij} \left( EBASIR_j - \overline{EBASIR} \right) \left( EBASIR_i - \overline{EBASIR} \right)}{\left( \sum_{j=1}^{n} \left( EBASIR_j - \overline{EBASIR} \right)^2 \right) \left( \sum_{j=1}^{n} \sum_{i=1}^{n} w_{ij} \right)}$$

where $n$ is the number of municipalities and $w_{ij}$ is a measure of spatial proximity between municipality i and j defined by whichever municipality $j$ is a neighbor of municipality $i$, and zero otherwise. This measure can vary between -1 and 1, negative values of I indicate negative spatial autocorrelation – neighboring values tend to be dissimilar – and positive values of I indicate positive autocorrelation – neighboring values tend to be similar. Values of I close zero indicate that there is no spatial structure (random spatial pattern). The local Moran Index is given by:

$$I_j = \frac{n \left( EBASIR_j - \overline{EBASIR} \right)}{\sum_{j=1}^{n} \left( EBASIR_j - \overline{EBASIR} \right)^2} \sum_{i}^{n} w_{ij} \left( EBASIR_i - \overline{EBASIR} \right), i \neq j$$

The positive correlation occurs when regions with high (or low) EBASIR tend to be adjacent to other regions with high (or low) EBASIR – high-high or low-low clusters – and negative correlation occurs when regions with high (or low) EBASIR tend to be adjacent to low (or high) EBASIR – high-low or low-high clusters.

The Moran Index was also applied to the municipality changes between 2000 and 2010 $(\beta_1)$ to identify municipality clusters with high-high or low-low values (positive spatial autocorrelation) of increase or decrease temporal trends on EBASIR.

A geographic information system (GIS) was used to visualize the distribution of the $EBASIR_t$ (in 2000 and in 2010), the pattern of the temporal trend between 2000 and 2010, and the LISA for both measures by sex.

The annual time series of HF ASIR for Continental Portugal by sex was also computed and smoothed with the following generalized additive model (GAM) model:

$ASIR_t \sim N(\mu_t, \sigma)$

$$log(\mu_t) = \beta_0 + s(Year^{(t)})$$

to identify shape and points where the temporal trend of ASIR changed significantly in magnitude and/or direction during the study period. Changes were quantified between turning points (or between turning points and extremes, in the case of the first and last period) of the time series.

The Statistical Analysis was performed using the statistical software R version 2.14.1 (Project for Statistical Computing) [20] and visualization was performed by ArcView 10.1.

**Results**

Our final population includes 96,905 admissions where 77.3% were in women, of patients aged 50 years and over, with a discharge diagnosis of HF caused by traumas of low/moderate energy (excluding readmissions and pathological fractures) in Continental Portugal between 2000 and 2010 (Figure 1). On average, women were older than men at admission (p<0.001), with a mean age (standard deviation – SD) of 81.2 (8.5) versus 78.2 (10.1) years old (Figure 2). The age-specific incidence rates increase exponentially with age (Figure 3).

**Figure 1 – Flow chart of data selection**

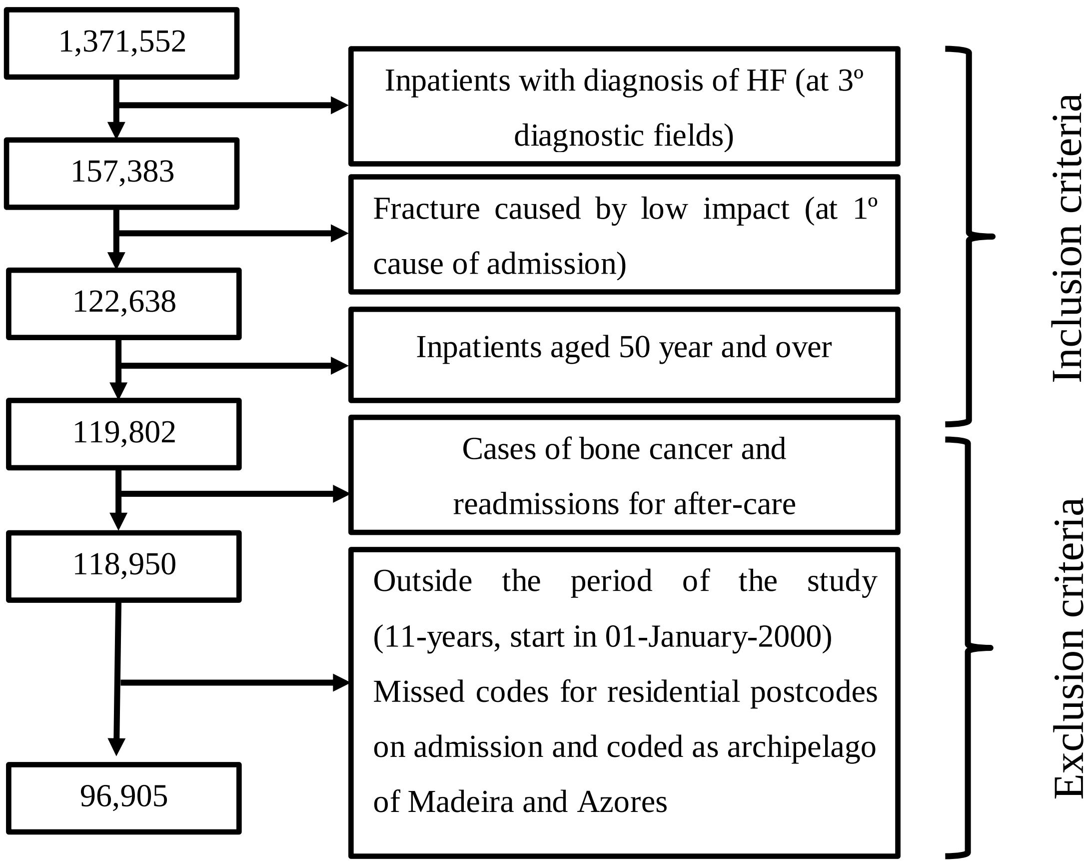


**Figure 2 – Absolute number of hip fracture by sex and age group (2000-2010)**

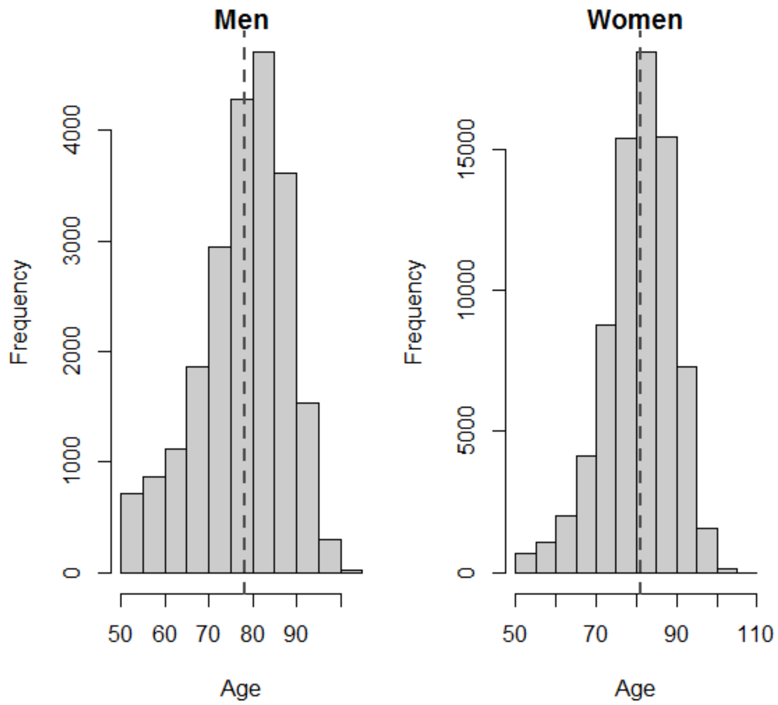
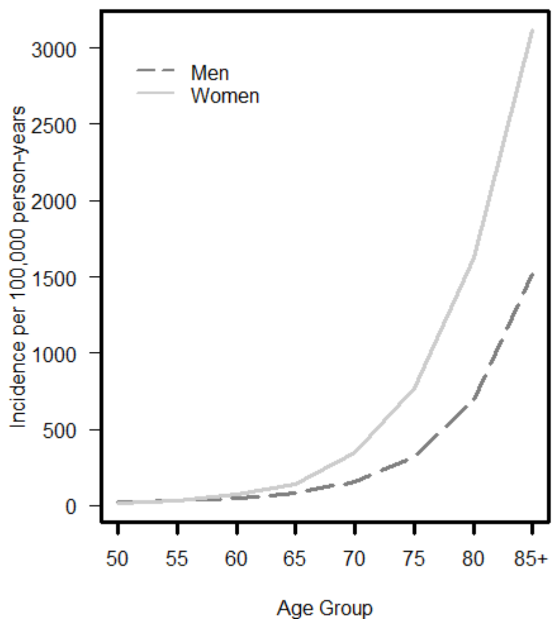



**Figure 3 – Age-specific incidence rates of hip fracture by sex (2000-2010)**

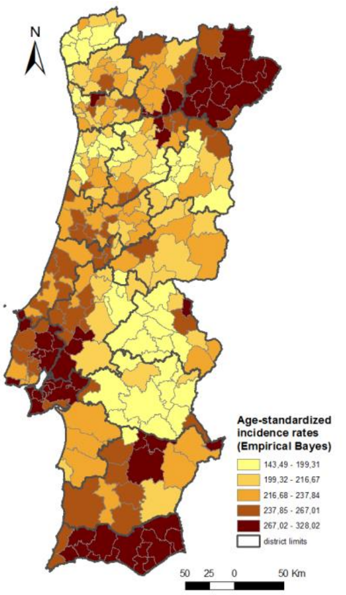



A higher proportion of municipalities presented a pattern of decrease between 2000 and 2010 in ASIR in women, especially on the coast and in the northeast, while in men there was a pattern of increase, especially in the inner central municipalities (Figure 4).

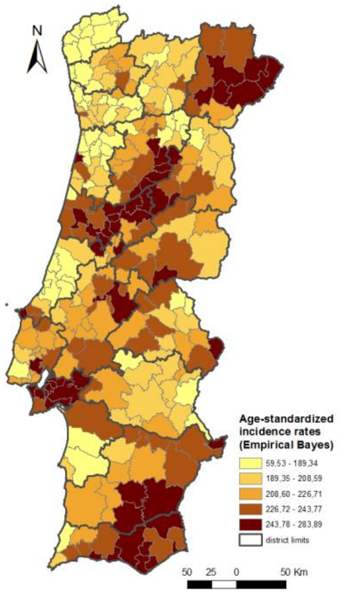
**Figure 4 – Empirical Bayes of age-standardized incidence rates of hip fracture by sex in 2000 and in 2010 and the slope of temporal trend between 2000 and 2010**

**Women**

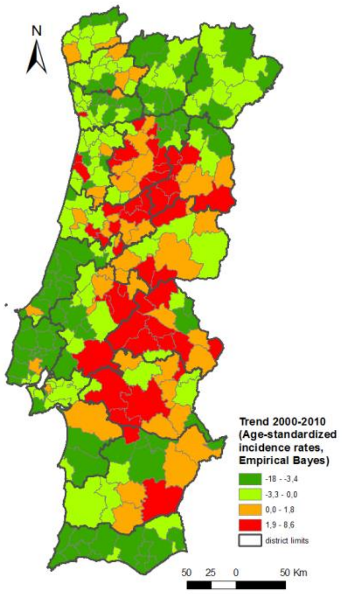
**2000**




**2010**

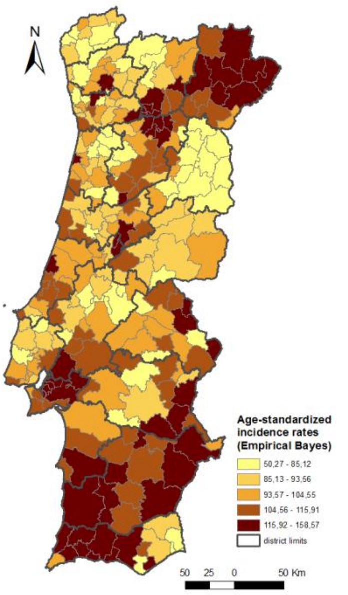



**Slope**

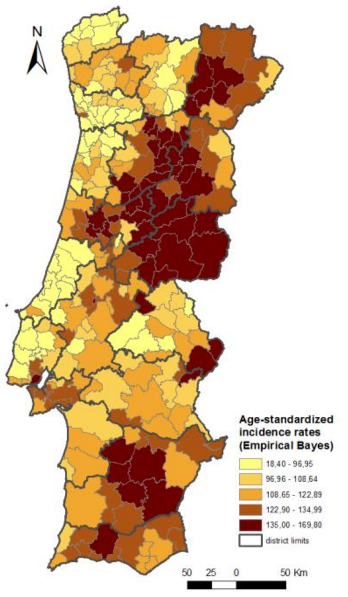



**Men**

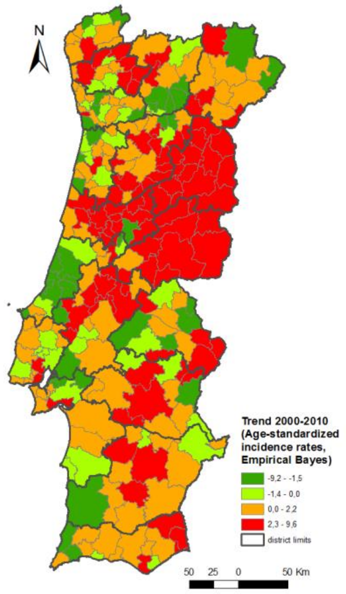
**2000**




**2010**




**Slope**

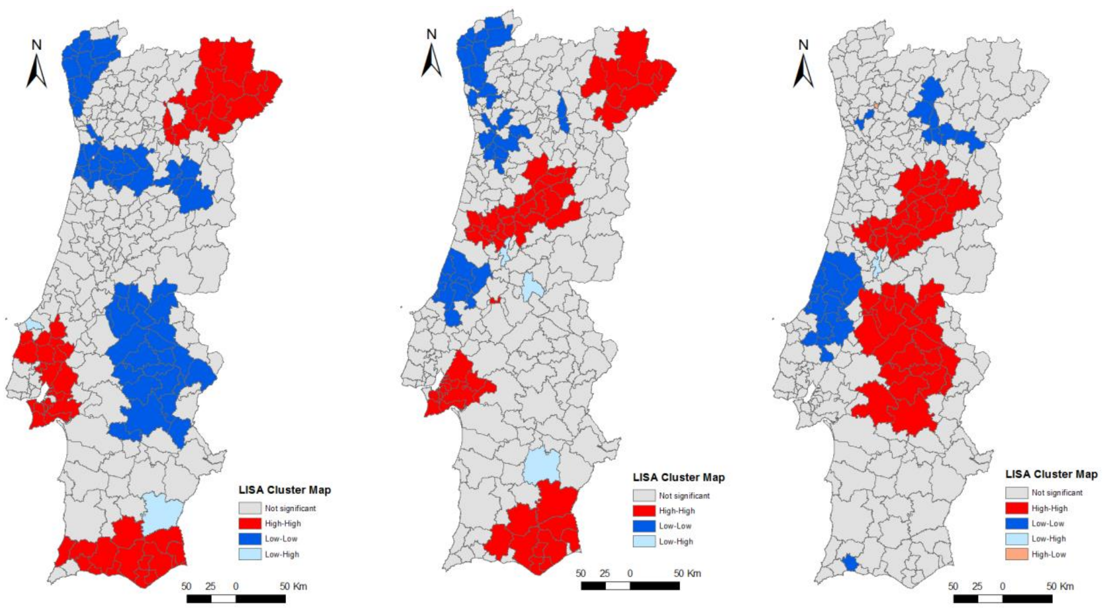


The global Moran index was highly significant for ASIR in 2000 (women: I=0.658, men: I=0.531) and in 2010 (women: I=0.664, men: I=0.672) and for the slope between 2000 and 2010 (women: I=0.538, men: I=0.530); indicating that neighboring districts had closer ASIR and slopes than distant ones. The local Moran index suggests two big clusters of high-high ASIR in the northeast and south for women, in both years 2000 and 2010, and two big clusters of high-high in the coastal southern area and in the northeast for men, in 2000; in 2010, the northeastern cluster observed in 2000 moved, in terms of latitude, to lower regions. One bigger cluster low-low ASIR was suggested for women in 2000 in the central inland region, but it disappeared in 2010 (Figure 5). Clusters of high-high slope (clusters of increase) were found in ASIR between 2000 and 2010 in the central inland area and clusters of low-low slope (clusters of decrease) were observed in the central coastal region for both sexes.

**Figure 5 – Local indicators of spatial association of empirical Bayes of age-standardized incidence rates of hip fracture by sex in 2000 and in 2010 and the slope of temporal trend between 2000 and 2010**

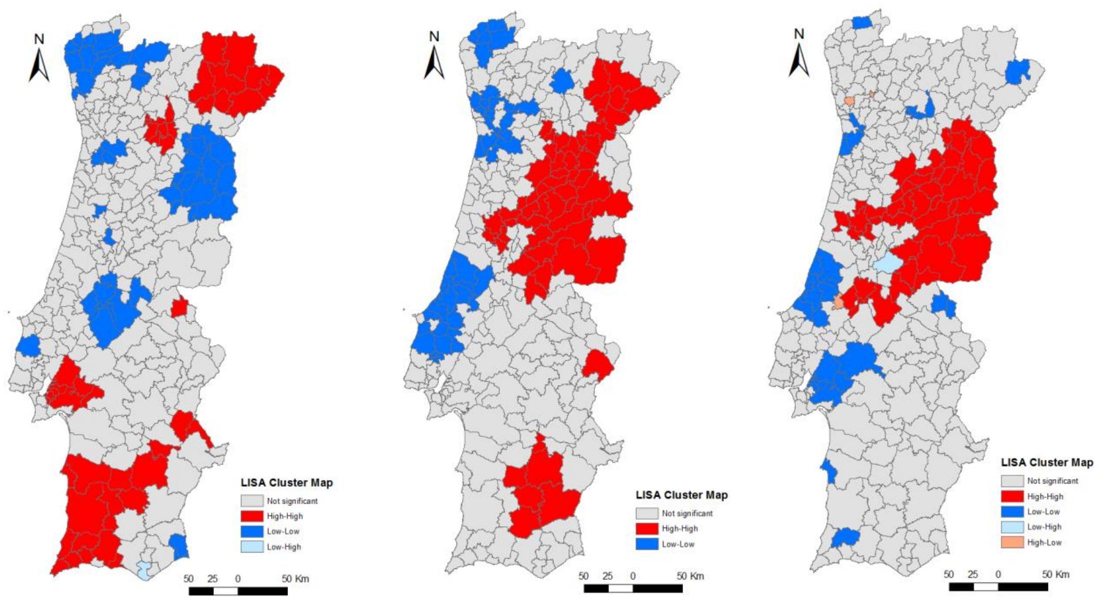
**Women**

| 2000 | 2010 | Slope |
|---|---|---|




**Men**

| 2000 | 2010 | Slope |
|---|---|---|



Changes in the temporal trends in the absolute number and in ASIR by sex are shown in Figure 6. The absolute number increased in the overall period while the ASIR decreased between 2002 and 2007, followed by an increase. The estimated overall ASIR for Continental Portugal was 107.5 (95%CI 102.4–112.7) and 222.5 (95%CI 216.7–228.3) per 100,000 person-years, in 2000, and 110.4 (95%CI 105.9–115.2) and 223.3 (95%CI 218.1–228.6) in 2010, respectively, in men and women. However, a period of decrease was observed between 2002 and 2007. In 2010, the ASIR returned to the same value as in 2000, which means if a constant rate of change within the period is assumed, no changes would be observed during the period.

**Figure 6 – Trends of absolute number (A) and age-standardized incidence rates (B) of hip fracture (95% confidence interval) by sex (2000-2010)**

## Discussion

A higher geographic heterogeneity of age-standardized incidence rates of HF over time and across municipalities between 2000 and 2010 was identified in Portugal in our study. The ASIR was higher in the northeast and the south for both sexes. In women, a higher incidence of ASIR around Lisbon was observed in 2000, which attenuates in 2010. In men, a lower incidence in the central inland region was observed in 2000, which aggravates in 2010. Women present a decrease in age-standardized incidence rates in almost all municipalities, except for inland municipalities, while men present an increase in almost all municipalities, especially for inland municipalities. The global Moran index shows a significant positive spatial autocorrelation for ASIR and for slope between 2000 and 2010 for both sexes, being higher in women than in men in both cases, indicating that proximity areas tend to be more similar than distant areas in ASIR and in slope. For women, clusters of high-high ASIR were found in the northeast and the south whereas they were found in the coastal southern area and the northeast for men. Clusters of increase in ASIR (high-high slope) between 2000 and 2010 were found in the central inland while clusters of decrease (low-low slope) were observed in the central coast for both sexes. In Continental Portugal, between 2000 and 2010, an overall increasing trend in the absolute number of HF was observed and no significant changes in age-standardized incidence rates were observed for either sex (if a constant rate of change is assumed within the period), although differences in trends by municipalities seems to exist for both sexes.

The underlying reason for this geographic heterogeneity is unknown; however, genetic, socioeconomic, territorial occupation and environmental factors might explain part of the spatial variability. Portugal is not so heterogeneous regarding genetic factors so that this factor cannot reasonably explain this spatial pattern by itself [21-23]. Socioeconomic status is associated with the degree of physical activity and nutrition quality [24]. It is well known the effect of nutrition in enhancing the peak bone mass in children and adolescents and to reduce the risk of fractures, especially in the elderly and post-menopausal women [25]. There is evidence that physical activity increases bone mass, density and strength, which prevents osteoporosis and falling, consequently preventing HF [26]. Studies show that regions with a high level of social deprivation present a higher deficient in access to health care and preventive actions, which might lead to a higher risk of osteoporosis and HF in this population [27].

Several studies in the literature reported a one- or two-decade decrease [28, 29] after a long period of increase [30]. A decreasing trend over the last decades has been reported in Scandinavian countries such as Denmark [31], Sweden [32], Finland [33] and Norway [34], also in France [35], Spain [36], Switzerland [37] and Netherlands [38] and most recently, in Austria [39] and Greece [40]. In Portugal, a decreasing trend in the HF was observed after 2003 for women [11]. High variability has been reported within the country and also within subgroups of the population, such as sex and age group [11, 29, 41]. Hip fracture occurrences are more common in women than in men probably due to the high susceptible of osteoporosis disease in women, although a larger decrease has been described in women compared to men in some studies [28, 29] and differences within age groups have even been reported. Women aged 60-75 presented a higher decrease when compared to other age groups [11]. This might be due to a preventive intervention focus more common in women and on a particular target age group. Preventive intervention might explain differences in trends by municipalities between sexes and also within sexes and age groups. Differences in access to intervention programs between municipalities probably have different impacts on HF incidence by municipalities in both sexes and age groups. Differences in the temporal trend might also be a result of cohort or period effects reflecting important changes in population: such as improved nutrition and better maternal health; improved prevention strategies against osteoporosis, both medical (pharmaceutical treatment) and non-medical (prevention of falls) in recent years [11, 42, 43]; and changes in the political and economic regime that may have affected the health of the population and/or access to healthcare [44]. In Portugal, surprising results revealed fluctuations in risk of HF, coincident with all the major political and economic changes in the first half of the 20th century in Portugal [44] and the abrupt decrease observed after 2003 are coincident with the abrupt increase in bisphosphonate sales [11].

Environmental factors might also explain part of the spatial variability or even might explain some spatial-temporal pattern of HF risk, probably some of the high incidence in particular regions and/or time might be consequence of environmental factors, such as weather conditions that might increase the susceptibility of falling or promote less activity and less synthesis of vitamin D, due to more adverse weather conditions or even the drinking water composition as it is known that high exposure or a long exposure to low levels of heavy metals or mineral might promote deterioration or might be beneficial for bone formation [45].

A limitation of our study is that registries do not record a code for each patient, but instead a code for each admission, due to confidentiality issues, and this prevents the identification of recurrent fractures. However, our study focuses on incidence rates of HF (number of HF in a population at risk) rather than cumulative incidence (number of persons with an HF in a population at risk) and, therefore, such a limitation does not bias our results. Our study benefits from the advantage of using population-based longitudinal data from a nationwide registry.

## Conclusions

This study is an exploratory analysis and the causes behind the differences over time and across regions need further investigation. The underlying causes of HF risk are multifactorial; individuals and ecological factors might play an important role in this process. The social and economic burden of hip fractures reinforces the importance of more epidemiological studies to understand the spatial and temporal patterns of HF risk and to identify populations at higher risk to help decision-makers develop more effective interventions and treatment programs.

## References

1. Kanis JA, Oden A, McCloskey EV, Johansson H, Wahl DA, Cooper C. A systematic review of hip fracture incidence and probability of fracture worldwide. Osteoporosis international: a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA. 2012;23(9):2239-56. Epub 2012/03/16.

2. Castro da Rocha FA, Ribeiro AR. Low incidence of hip fractures in an equatorial area. Osteoporosis international : a journal established as result of

cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA. 2003;14(6):496-9. Epub 2003/05/06.

3. Litwic A, Edwards M, Cooper C, Dennison E. Geographic differences in fractures among women. Womens Health (Lond Engl). 2012;8(6):673-84. Epub 2012/11/28.

4. de Pina MF, Alves SM, Barbosa M, Barros H. Hip fractures cluster in space: an epidemiological analysis in Portugal. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA. 2008;19(12):1797-804. Epub 2008/06/10.

5. Kanis JA, Johnell O, De Laet C, Jonsson B, Oden A, Ogelsby AK. International variations in hip fracture probabilities: implications for risk assessment. Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research. 2002;17(7):1237-44. Epub 2002/07/05.

6. Oliveira CM, Economou T, Bailey T, Mendonca D, Pina MF. The interactions between municipal socioeconomic status and age on hip fracture risk. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA. 2015;26(2):489-98. Epub 2014/10/26.

7. King AB, Tosteson AN, Wong JB, Solomon DH, Burge RT, Dawson-Hughes B. Interstate variation in the burden of fragility fractures. Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research. 2009;24(4):681-92. Epub 2008/12/10.

8. Ballane G, Cauley JA, Luckey MM, Fuleihan Gel H. Secular trends in hip fractures worldwide: opposing trends East versus West. Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research. 2014;29(8):1745-55. Epub 2014/03/20.

9. Lofman O, Berglund K, Larsson L, Toss G. Changes in hip fracture epidemiology: redistribution between ages, genders and fracture types. Osteoporosis

international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA. 2002;13(1):18-25. Epub 2002/03/07.

10. Huusko TM, Karppi P, Avikainen V, Kautiainen H, Sulkava R. The changing picture of hip fractures: dramatic change in age distribution and no change in age-adjusted incidence within 10 years in Central Finland. Bone. 1999;24(3):257-9. Epub 1999/03/11.

11. Alves SM, Economou T, Oliveira C, Ribeiro AI, Neves N, Gomez-Barrena E, et al. Osteoporotic hip fractures: bisphosphonates sales and observed turning point in trend. A population-based retrospective study. Bone. 2013;53(2):430-6. Epub 2013/01/01.

12. Icks A, Haastert B, Wildner M, Becker C, Meyer G. Trend of hip fracture incidence in Germany 1995-2004: a population-based study. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA. 2008;19(8):1139-45. Epub 2007/12/19.

13. Melton LJ. Why are hip fracture rates falling? Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research. 2007;22(7):1096; author reply 7. Epub 2007/03/21.

14. ACSS. Auditoria da codificação clínica [Clinical codification Audits]. 2011 Available from: http://portalcodgdh.min-saude.pt/index.php/Auditoria_da_codificação_cl%C3%ADnica.

15. INE. *Instituto Nacional de Estatística*; [cited 2012]; Available from: www.ine.pt.

16. Eurostat, Statistical Office of the European Communities, Unit population and social condition. L-2920 Luxembourg. [cited Accessed February 3, 2012].

17. Buescher P. Problems with Rates Based on Small Numbers. Statistical Primer. 2008(12).

18. Bailey T, Gatrell A. Interactive Spatial Data Analysis. Harlow, editor: Longman Scientific and Technical.; 1995.

19. Bailey T, Gatrell A. Interactive Spatial Data Analysis. Longman, editor1995.

20. R-Core-Team. R: A language and environment for statistical computing. Vienna, Austria2014.

21. Pereira L, Prata M, Amorim A. Diversity of mtDNA lineages in Portugal: not a genetic edge of European variation. Ann Hum Genet. 2000;64:491-506.

22. Pereira R, Fondevila M, Philips C, Amorim A, Carracedo A, Gusmao L. Genetic characterization of 52 autosomal SNPs in the Portuguese population. Forensic Science International, Genetics Supplement Series. 2008;1:358-60.

23. Beleza S, Gusmao L, Lopes A. Micro-phylogeographic and demographic history of Portuguese male lineages. Ann Hum Genet. 2006;70:181-94.

24. Hernlund E, Svedbom A, Ivergard M, Compston J, Cooper C, Stenmark J, et al. Osteoporosis in the European Union: medical management, epidemiology and economic burden. A report prepared in collaboration with the International Osteoporosis Foundation (IOF) and the European Federation of Pharmaceutical Industry Associations (EFPIA). Archives of osteoporosis. 2013;8(1-2):136. Epub 2013/10/12.

25. Prentice A. Diet, nutrition and the prevention of osteoporosis. Public health nutrition. 2004;7(1A):227-43. Epub 2004/02/20.

26. Kannus P. Preventing osteoporosis, falls, and fractures among elderly people. Promotion of lifelong physical activity is essential. BMJ. 1999;318(7178):205-6. Epub 1999/01/23.

27. West J, Hippisley-Cox J, Coupland CA, Price GM, Groom LM, Kendrick D, et al. Do rates of hospital admission for falls and hip fracture in elderly people vary by socio-economic status? Public Health. 2004;118(8):576-81. Epub 2004/11/09.

28. Leslie WD, O'Donnell S, Jean S, Lagace C, Walsh P, Bancej C, et al. Trends in hip fracture rates in Canada. Jama. 2009;302(8):883-9. Epub 2009/08/27.

29. Kannus P, Niemi S, Parkkari J, Palvanen M, Vuori I, Jarvinen M. Nationwide decline in incidence of hip fracture. Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research. 2006;21(12):1836-8. Epub 2006/09/28.

30. Dhanwal DK, Dennison EM, Harvey NC, Cooper C. Epidemiology of hip fracture: Worldwide geographic variation. Indian journal of orthopaedics. 2011;45(1):15-22. Epub 2011/01/12.

31. Abrahamsen B, Vestergaard P. Declining incidence of hip fractures and the extent of use of anti-osteoporotic therapy in Denmark 1997-2006. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA. 2010;21(3):373-80. Epub 2009/05/14.

32. Nilson F, Moniruzzaman S, Gustavsson J, Andersson R. Trends in hip fracture incidence rates among the elderly in Sweden 1987-2009. J Public Health (Oxf). 2013;35(1):125-31. Epub 2012/07/04.

33. Korhonen N, Niemi S, Parkkari J, Sievanen H, Palvanen M, Kannus P. Continuous decline in incidence of hip fracture: nationwide statistics from Finland between 1970 and 2010. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA. 2013;24(5):1599-603. Epub 2012/10/31.

34. Omsland TK, Holvik K, Meyer HE, Center JR, Emaus N, Tell GS, et al. Hip fractures in Norway 1999-2008: time trends in total incidence and second hip fracture rates: a NOREPOS study. European journal of epidemiology. 2012;27(10):807-14. Epub 2012/08/09.

35. Maravic M, Taupin P, Landais P, Roux C. Change in hip fracture incidence over the last 6 years in France. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA. 2011;22(3):797-801. Epub 2010/06/03.

36. Arias LH, Treceno C, Garcia-Ortega P, Rodriguez-Paredes J, Escudero A, Sainz M, et al. Hip fracture rates and bisphosphonate consumption in Spain. An ecologic study. European journal of clinical pharmacology. 2013;69(3):559-64. Epub 2012/07/24.

37. Lippuner K, Popp AW, Schwab P, Gitlin M, Schaufler T, Senn C, et al. Fracture hospitalizations between years 2000 and 2007 in Switzerland: a trend analysis. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA. 2011;22(9):2487-97. Epub 2010/12/15.

38. Hartholt KA, Oudshoorn C, Zielinski SM, Burgers PT, Panneman MJ, van Beeck EF, et al. The epidemic of hip fractures: are we on the right track? PloS one. 2011;6(7):e22227. Epub 2011/07/30.

39. Mann E, Icks A, Haastert B, Meyer G. Hip fracture incidence in the elderly in Austria: an epidemiological study covering the years 1994 to 2006. BMC geriatrics. 2008;8:35. Epub 2008/12/25.

40. Lyritis GP, Rizou S, Galanos A, Makras P. Incidence of hip fractures in Greece during a 30-year period: 1977-2007. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA. 2013;24(5):1579-85. Epub 2012/10/16.

41. Cooper C, Cole ZA, Holroyd CR, Earl SC, Harvey NC, Dennison EM, et al. Secular trends in the incidence of hip and other osteoporotic fractures. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA. 2011;22(5):1277-88. Epub 2011/04/05.

42. Feder G, Cryer C, Donovan S, Carter Y. Guidelines for the prevention of falls in people over 65. The Guidelines' Development Group. Bmj. 2000;321(7267):1007-11. Epub 2000/10/20.

43. Melton LJ, 3rd, Kanis JA, Johnell O. Potential impact of osteoporosis treatment on hip fracture trends. J Bone Miner Res. 2005;20(6):895-7. Epub 2005/05/11.

44. Alves SM, Castiglione D, Oliveira CM, de Sousa B, Pina MF. Age-period-cohort effects in the incidence of hip fractures: political and economic events are coincident with changes in risk. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA. 2014;25(2):711-20. Epub 2013/08/29.

45. Aaseth J, Boivin G, Andersen O. Osteoporosis and trace elements--an overview. J Trace Elem Med Biol. 2012;26(2-3):149-52. Epub 2012/05/12.

## 3.2 The interactions between municipality socioeconomic status and age on hip fracture risk

Article published in Osteoporosis International

February 2015, Volume 26, Issue 2, pp 489-98.

DOI: 10.1007/s00198-014-2869-0.

Date 2014 Oct 25

# THE INTERACTIONS BETWEEN MUNICIPAL SOCIOECONOMIC STATUS AND AGE ON HIP FRACTURE RISK

**Oliveira CM, Economou T, Bailey T, Mendonça D, Pina MF**

**Carla Maria Oliveira**

Rua do Campo Alegre, 823, 4150-180 Porto, INEB, Instituto de Engenharia Biomédica, Portugal

Rua das Taipas 135, 4050-600, Porto, ISPUP, Instituto de Saúde Pública da Universidade do Porto, Portugal

Al. Prof. Hernâni Monteiro, 4200 - 319 Porto, Departamento de Epidemiologia Clínica, Medicina Preditiva e Saúde Pública, Faculdade de Medicina da Universidade do Porto, Portugal

carlaoliveir@gmail.com

**Theodoros Economou**

College of Engineering, Mathematics and Physical Sciences, University of Exeter, North Park Road, EX4 4QF, Exeter, UK.

t.economou@ex.ac.uk

**Trevor Bailey**

College of Engineering, Mathematics and Physical Sciences, University of Exeter, North Park Road, EX4 4QF, Exeter, UK.

t.c.bailey@ex.ac.uk

**Denisa Mendonça**

Rua das Taipas 135, 4050-600, Porto, ISPUP, Instituto de Saúde Pública da Universidade do Porto, Portugal

Rua de Jorge Viterbo Ferreira n.º 228, 4050-313 Porto, ICBAS, Instituto de Ciências Biomédicas Abel Salazar da Universidade do Porto
dvmendon@icbas.up.pt

**Maria Fátima Pina**
Al. Prof. Hernâni Monteiro, 4200 - 319 Porto, Departamento de Epidemiologia Clínica, Medicina Preditiva e Saúde Pública, Faculdade de Medicina da Universidade do Porto, Portugal
Rua do Campo Alegre, 823, 4150-180 Porto, INEB, Instituto de Engenharia Biomédica, Portugal
Rua das Taipas 135, 4050-600, Porto, ISPUP, Instituto de Saúde Pública da Universidade do Porto, Portugal
fpina@med.up.pt

**Corresponding author**: C Oliveira; carlaoliveir@gmail.com; phone +351966060193; Fax: 351 226094567; Rua do Campo Alegre, 823, 4150-180 Porto, INEB, Instituto de Engenharia Biomédica, Portugal

**Acknowledgments**: This work was supported by FEDER funds through the Programa Operacional Factores de Competitividade (COMPETE) and by Portuguese funds through Fundação para a Ciência e a Tecnologia (FCT) within the framework of the project PTDC/SAU-EPI/113424/2009 grant.
We also acknowledge the Central Administration of Health Services (ACSS) for the data from the National Hospital Discharge Register.

**Conflict of Interest**: Carla Maria Oliveira, Theodoros Economou, Trevor Bailey, Denisa Mendonça and Maria Fátima Pina declare that they have no conflict of interest.

**Role of funding source**: The funder Fundação para a Ciência e Tecnologia - FCT has no role in this paper.

**Mini-abstract**

Age modifies the effect of area-level socioeconomic status (SES) in the risk of fragility hip fractures (HF). For oldest individuals, the risk of HF increases as SES increases. For youngest, risk of HF increases as SES decreases. Our study may help to implement political decisions and medical guidelines for HF prevention.

## ABSTRACT

**Background:** The effect of socioeconomic status (SES) on hip fracture (HF) incidence remains unclear.

**Objective:** To evaluate the association between HF incidence and municipality-level SES but also any interactions between age and SES.

**Methods:** From the Portuguese Hospital Discharge Database we selected hospitalizations (2000-2010) of patients aged 50+, with HF diagnosis (codes 820.x, ICD9.CM), caused by traumas of low/moderate energy, excluding bone cancer cases and readmissions for after-care. Municipalities were classified according to SES (deprived to affluent) using 2001 Census data. A spatial Bayesian hierarchical regression model (controlling for data heterogeneity effect and spatial autocorrelation), using the Poisson distribution, was used to quantify the Relative Risk (RR) of HF, 95% credible interval (95%CrI), and to analyze the interaction between age and SES, after allowing for rural conditions.

**Results**: There were 96,905 HF, 77.3% of which were women who on average were older than men (mean age 81.2±8.5 vs 78.2±10.1 years) at admission ($p<0.001$). In women, there was a lower risk associated with better SES: RR=0.83 (95%CrI 0.65-1.00) for affluent versus deprived. There was an inverse association between SES and HF incidence rate in the youngest and a direct association in the oldest, for both sexes, but significant only between deprived and affluent in older ages (≥75years).

**Conclusions**: Interaction between SES and age may be due to inequalities in lifestyles, access to health systems and preventive actions. These results may help decision-makers to better understand the epidemiology of hip fractures and better direct the implementation of political decisions.


**Keywords**: osteoporosis, hip fractures, socioeconomic status, spatial epidemiology, interaction

## Introduction

Bone fractures in the elderly[1] are mainly caused by a combination of low bone mineral density (BMD) in individuals with osteoporosis, and traumas of low/moderate energy after a fall from standing height or less, and they are more frequent among women [2]. From all such fragility fractures, hip fractures (HF) are the most severe, because of the high costs associated with treatment and recovery [3] and the high physical disability, social dependence and mortality among the elders after a fracture [2, 4].

In Europe, incidence rates of HF are seven times higher in the northern countries when compared to the southern countries [5], although when analyzing the incidence of HF at municipality level, there are strong geographical differences within the countries - in Portugal incidence rates of HF in the northeast and south of the country are similar to those reported in Finland [6]. The reasons for such geographical differences are not well understood but a plausible explanation is that such differences are associated with socioeconomic and environmental contexts [7]: geographical variations in diet, body height and weight, smoking, alcohol intake, physical activity and uptake of anti-osteoporosis medication [2] can be associated with HF incidence and may explain the geographical differences in the incidence rates. Heterogeneity in the policy framework, service provision and service uptake for osteoporotic fracture may be also a reason for the difference in HF risk between regions [8]. In addition, unhealthy lifestyles and exposure to environmental risk factors tend to be higher in deprived areas [9].

Unfortunately, relatively little work has been published regarding the association between HF risks and socioeconomic status (SES) or some proxy:

Studies consistently showed a significant association with marital status (a decrease in those married or living with someone) [10-12], occupational category (reduced risk for employed vs unemployed and for tradespeople vs laborers) [13, 14] and residence type (living in large vs small homes decreases the risk) [11]. In a study in Stockholm [10, 11, 15], indicated reduced risk for those with medium or high incomes compared to low. For Australia, [16], there was reduced risk for those with private health insurance compared to ones without. In the Trend region (UK) study, an increased risk of falls in areas of lower SES (for adults aged 75 years or over) was described but no significant association with HF [7]. Nevertheless, some inconsistencies do exists, for example, the role of income or education in the risk of HF: there were different associations in different age groups, which might suggest an age interaction with SES [17].

The age modifiable effect on the association between SES and HF is not well studied in the current literature. A nationwide case-control study in Denmark described a reduction in the risk of any type of fracture in younger age groups (<40 years old) among those with higher education levels while the opposite was observed among subjects aged 60 years or more: higher risk in the higher education levels [18]. In Wales, those over 74 years-old living in affluent neighborhoods have greater risk compared with those living in more deprived areas, while individuals below 74 living in more deprived areas, had an increased risk of HF when compared with those living in more affluent areas [15, 19]. In the Stockholm metropolitan area, a higher risk of HF was found in the elderly living in more affluent areas, corroborating these findings. [18]

A better understanding of the relationship between HF and socioeconomic and environmental factors and their interactions with age can help in better targeting prevention measures of HF [7]. However, there is a gap in the scientific literature regarding this issue. Our objective here is to investigate and quantify the relationship between HF and SES as well as the relevance of the interaction between age and SES on HF incidence, in Portugal, using data in the period 2000-2010. To this end, we propose a flexible statistical model, which accounts for spatial heterogeneity in the data while also allowing for unobserved but also observed factors in the form of predictors.

**Materials and Methods:**

**Study area**

The study area is Continental Portugal, which had 10,057,999 inhabitants in 2010, distributed heterogeneously throughout 278 municipalities, with a median of 15,741 inhabitants per municipality. The less populated municipality has 1,836 inhabitants and the most populated are the capital, Lisbon, with 548,422 inhabitants. The population over the age of 50 rose from 3,298,900 (in 2000) to 3,789,091 (in 2010)[20]. In

Portugal, although it is a developed country, inequality of wealth distribution, measured through the GINI index, is among the highest in the European region [21].

**Data**

We used data from the National Hospital Discharge Register (NHDR), which has been mandatory for all Portuguese public hospitals since 1997 and whose quality is assessed regularly by internal (hospitals) and external (ACSS – Central Administration of the National System) auditors [22]. Each record in the NHDR corresponds to one discharge and contains information such as sex; age; first cause of admission and main diagnosis (and up to 19 secondary causes and 19 secondary diagnoses), coded according to the International Classification of Diseases, version 9, Clinical Modification (ICD9-CM); municipality of patient's residence; date of admission and discharge, hospital to and hospital from whenever there is a transfer between hospitals, among others [23]. In Portugal, access to the national health-care system is universal and tendentiously free-of-charge: contributions are based upon citizens' social and economic conditions [22]. All the patients with a hip fracture are hospitalized for treatment and due to the high costs involved, HF is primarily treated in public hospitals. Therefore, the admissions registered in the NHDR represent almost the totality nationwide.

We selected all hospital admissions, from 1 January 2000 to 31 December 2010, of patients aged 50 years and over, with a discharge diagnosis of HF (ICD9-CM codes 820.x) caused by traumas of low/moderate energy (ICD9-CM codes E849.0, E849.7 and E880-E888). We excluded readmissions (ICD9-CM codes 996.4 and V54.x) and pathological fractures (ICD9-CM codes 170.x and 171.x). No such data was available for the two autonomous regions, the archipelagos of the Azores or Madeira, and therefore, they were not included in the study (representing 5% of the Portuguese population). Counts of HF were stratified by the municipality of patient's residence, admission year, sex and 5-year age group (50-54… 80-84, 85+).

To calculate the population at-risk or person-years we aggregated data per municipality, sex and 5-year age groups using population data from the 2001 Census and from the annual official estimates for all the other years (INE - Statistics Portugal [20]).

The socioeconomic characterization of municipalities was based on data from the last available Census - 2001 (INE - Statistics Portugal [20]). In Portugal, there were no significant changes in SES during the study period and therefore, the relative position in the SES rank of municipalities between 2000 and 2010 remains stable (results not shown); each municipality was characterized by a set of variables related to buildings, households, families, and individuals. The variables included were: proportion of population by age groups and sex; proportion of retired individuals (by sex); proportion of widows; proportion of individuals receiving social support; proportion of illiteracy; ageing and youth dependency indexes; proportion of individuals living alone; mean number of rooms per household; mean number of individuals per household; unemployment rate; proportion of subjects with higher and basic education; proportion of subjects by category of occupation (managers/professionals/technicians; services/sales workers; skilled agricultural/plant & machine operators); income; proportion of residences and buildings with/without public water supply, mains or otherwise; and proportion of households with heating, by type of heating. To create the SES index, we performed a principal component analysis to reduce the set of variables described above to four components, which explained 75.8% of the total variability. Afterward, we used the four components to develop a hierarchical cluster analysis [24], using the Ward´s method. We used three clusters of SES to analyze the association with HF incidence: affluent, medium and deprived (Figure 1). The affluent SES aggregates municipalities with the younger population, higher educational level, a higher percentage of employed individuals, good housing conditions (plumbing, heating and bathroom facilities and shower). The medium SES aggregates municipalities with population older than in an affluent group, higher illiteracy rate, low indices per capita, a higher percentage of individuals employed in agricultural, forestry and industry. The deprived SES aggregates municipalities with the highest percentage of elderly, the highest illiteracy rate, the highest rate of people living alone, the lowest level of education, the lowest indices per capita, higher percentage of individuals with rural activities, the highest percentage of house with no running water and no bathroom facilities and shower and the highest percentage of individuals receiving unemployment benefits.

The distribution of the population in Continental Portugal significantly differ per SES group ($p<0.001$). The median population per municipality increases with SES: 1,607 inhabitants (interquartile range (IQR) 1,207 – 2,402) in the deprived SES cluster; 3,473 inhabitants (IQR 2,386 – 6,285) in the medium SES cluster and 7,426 inhabitants (IQR 3,453 – 12,706) in the affluent SES cluster. [20].

We considered rural conditions as a possible confounder of the association between SES and HF incidence rate since rural areas can be associated with a lower risk of HF[25] and some rural regions may have lower SES. Therefore, we classified the municipalities as rural, urban and semi-urban (Figure 1) based on the official information available [20].

**Statistical analysis**

For individuals characteristics, differences in mean age by sex and SES were analyzed using ANOVA and the Tukey HSD test for multiple comparisons; statistical significance level (two-sided) was set at 5%.

To assess the relationship between mean HF incidence rates and SES, a spatial Bayesian hierarchical regression model was implemented. Age and rural conditions were included in the model as predictors to allow for the (possibly) different behavior of HF rate between various categories of age and rural conditions. An interaction term between age and SES was also included to capture the possible modifiable effect of age in the relation between SES and HF incidence. All analyses were performed separately for each sex.

We assumed that the number of HF, $NFrat_{ij}$, in a specific age group $i$ ($i = 1, \dots, 8$) and in a specific municipality $j$ ($j = 1, \dots, 278$) is distributed as a Poisson random variable with mean $\lambda_{ij} = NPop_{ij}\varrho_{ij}$ where $NPop_{ij}$ is the population in age group $i$ and municipality $j$, and $\varrho_{ij}$ is the incidence rate of HF per unit population in age group $i$ and municipality $j$; so that, for instance, the quantity $\varrho_{ij}/\varrho_{kj}$ is the relative risk (RR) of age group $i$ to reference age group $k$ ($k = 1, \dots, 8$). For each sex, the parameters of interest were estimate by the following model:

$$NFrat_{ij}|(\psi_j, \phi_j) \sim Pois(\lambda_{ij})$$

$$log(\lambda_{ij}) = log(NPop_{ij}) + log(\varrho_{ij}) = log(NPop_{ij}) + \beta_0 + \beta_1 AgGr_i + \beta_2 SES_j + \beta_3 RurUrb_j$$

$$+\beta_{12} AgGr_i * SES_j + \psi_j + \phi_j$$

$$\psi_j \sim N(0, \sigma_\psi^2)$$

$$\phi_j | \phi_{(-j)} \sim N(\bar{\phi}_j, \sigma_\phi^2/m_j); \;\; \phi_{(-j)} = \{\phi_k : \mathrm{k} \neq \mathrm{j} \wedge \mathrm{k} \in A_j\}$$

where $A_j$ is the set of neighbors of municipality $j$; the $AgGr_i$ is the age group $i$; the SES $(SES_j)$ and the rural condition $(RurUrb_j)$ are characteristics of the municipality $j$; $\psi_j$ is the non-spatial random effect and $\phi_j$ is the spatially structured random effect ($\bar{\phi}_j$ is the average of the $\phi_k$ that are adjacent to $\phi_j$ and $m_j$ is the number of these adjacencies). The joint model for the $\phi_j$'s is the so called conditional autoregressive (CAR) normal prior [26].

The model included two random effects (or latent variables) at the municipality level. One of the random effects ($\psi_j$) accounted for the unexplained heterogeneity in HF rate due to unobserved municipality-level factors while the other ($\phi_j$) allowed for spatially structured dependence in measurements of HF in municipalities that were spatially close. The latter relates to the fact that HF incidence in two nearby municipalities tends to be more similar (in terms of risk) than two areas chosen randomly.

The model described above was implemented in a Bayesian framework and estimated using Markov Chain Monte Carlo (MCMC). In this framework, parameters are treated as random variables whose "prior" distribution expresses the uncertainty about their value before any data is observed. After data is obtained, though, prior distributions (or simply priors), are combined with the data through Bayes theorem to produce the posterior distributions (or simply the posteriors) of each parameter. The posteriors express the uncertainty about model parameters after data is observed and all statistical inference is based solely on the posteriors. MCMC is a numerical technique which produces samples of values that eventually converge (after a certain "burn-in" number) to samples of values from the posterior (distribution) of each parameter.

Uninformative prior distributions were assumed for the model parameters. Parameters $\beta_0, \beta_1, \beta_2, \beta_3, \beta_{12}$ were given Gaussian priors with zero mean and large variance (1000) whereas $\sigma_\psi^2$ and $\sigma_\phi^2$ priors were assumed to be gamma distributed: gamma (0.5, 0.0005).

The RR and its 95% credible interval (95% CrI) were estimated using the sample mean and the 2.5% and 97.5% empirical quantiles of the posterior samples from each parameter of interest. These samples are based on two MCMC chains with 100,000 iterations each and a burn-in period of 10,000.

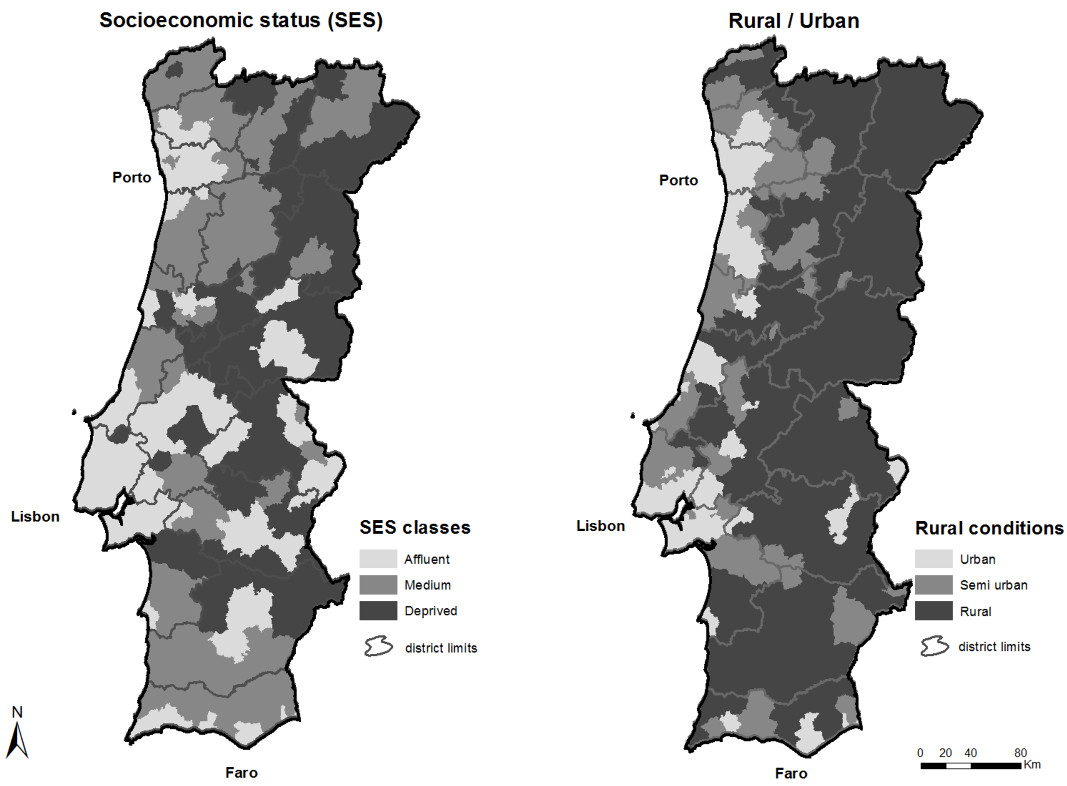
All the analyses were performed with the Statistical software R version 2.14.1 (Project for Statistical Computing)[27] and WinBUGS14 (WinBUGS14, Cambridge, UK)[28] using R2WinBUGS package to connect both tools. WinBUGS uses Gibbs sampling, a particular MCMC technique, to produce samples from the posterior distribution of each parameter (or simply posterior samples).

**Results:**

There were 98,186 admissions for HF in Continental Portugal between 2000 and 2010. From those we excluded 585 because of missing data for the municipality of residence and 696 because of readmissions for aftercare; our final sample includes 96,905 fractures of which 74,928 (77.3%) were in women. On average, women were older than men at admission ($p<0.001$), with a mean age (Standard Deviation – SD) of 81.2 (8.5) versus 78.2 (10.1) years old, and the same pattern was observed in all the SES; the highest age difference (3.3 years 95% CI: 3.0-3.5) between sexes was in the affluent municipalities and the lowest (2.5 years 95% CI: 2.0-3.1) was in the deprived municipalities (Table 1).

Ages differences between all SES were observed in both sexes, except between affluent and medium SES in women. Men and women were older at admission in the deprived SES and younger in the affluent SES; such differences in the mean age of admission between SES were higher in men (1.8 years 95% CI: 1.2-2.3) than in women (1.0 years (95% CI: 0.7-1.3) (Table 1).

**Figure 1 – Geographical distribution of socioeconomic status (SES) and rural conditions, by municipality**




The annual average of age-standardized incidence rates (per 100,000 inhabitants, 95% confidence intervals) of HF were 210 (207 - 212) for women and 102 (100 – 105 for men (direct method, 2006 European standard population). There is an accentuated geographic pattern, with the highest incidence rates in the northeast, and south of Portugal[6]. Table 2 shows the annual average of age-specific incidence rates of HF per SES and Sex. In general, youngest adults living in areas with higher SES had a lower risk of HF compared to those living in lower SES areas and the reverse occurs for the oldest individuals.

Initially, the main effect model was considered (not including interaction term: $\beta_{12} = 0$) and adjusting for age and rural conditions, the highest risk of HF was in the deprived SES areas in both sexes. Among women, there was a trend in HF incidence and SES: the risk decreased as the SES increased. Among men, such a trend was not observed (Table 1).

**Table 1 – Mean age (95% Confidence Intervals) at admission, absolute incidence (%) and Relative Risk of hip fracture (95%Credible Intervals) by sex and socioeconomic status (SES)**

| | Men | | | | Women | | | |
|---|---|---|---|---|---|---|---|---|
| Classes of SES | Mean age (95%CI) | n | (%) | RR* (95%CrI) | Mean age (95%CI) | n | (%) | RR* (95%CrI) |
| Deprived | 79.5 (79.1-79.8) | 2971 | 14 | Reference | 82.0 (81.8-82.2) | 9,660 | 13 | Reference |
| Medium | 78.4 (78.2-78.6) | 6,153 | 28 | 0.89 (0.64, 1.27) | 81.1 (81.0-81.2) | 19,421 | 26 | 0.91 (0.69, 1.15) |
| Affluent | 77.7 (77.5-77.9) | 12,853 | 58 | 0.90 (0.66, 1.33) | 81.0 (80.9-81.1) | 45,847 | 61 | 0.83 (0.65, 1.00) |
| Total | 78.2 (78.1-78.3) | 21,977 | | | 81.2 (81.1-81.3) | 74,928 | | |

CI – Confidence Intervals
CrI – Credible Intervals
n – absolute incidence
SES – Socioeconomic status
RR – Relative Risk
(*) Adjusted for age and rural conditions

**Table 2 – Age-specific incidence rates of hip fracture by sex and socioeconomic status (SES)**

| | | Age-specific incidence rates (95% CI) Age Group: | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Sex | SES | 50-54 | 55-59 | 60-64 | 65-69 | 70-74 | 75-79 | 80-84 | 85+ |
| Men | Most Affluent | 179.44 (170.76, 188.12) | 261.45 (250.7, 272.2) | 384.48 (370.50, 398.45) | 717.55 (697.63, 737.47) | 1276.29 (1248.93, 1303.64) | 2761.42 (2717.03, 2805.82) | 5415.74 (5341.66, 5489.83) | 13105.13 (12973.15, 13237.10) |
| | Moderate | 137.26 (126.54, 147.98) | 228.58 (213.87, 243.3) | 338.16 (319.31, 357.01) | 631.73 (605.45, 658.00) | 1141.64 (1105.40, 1177.88) | 2463.02 (2404.14, 2521.91) | 4782.08 (4684.69, 4879.47) | 11379.14 (11206.45, 11551.83) |
| | Most Deprived | 183.09 (159.12, 207.06) | 295.28 (264.19, 326.38) | 420.56 (384.94, 456.17) | 702.1 (658.67, 745.53) | 1038.76 (987.15, 1090.36) | 2136.89 (2057.92, 2215.86) | 4131.64 (4006.25, 4257.02) | 9633.16 (9415.14, 9851.18) |
| | Total | 197.74 (190.62, 204.87) | 299.24 (290.16, 308.33) | 447.9 (436.17, 459.64) | 807.99 (791.84, 824.15) | 1406.11 (1384.33, 1427.89) | 3023.64 (2988.52, 3058.75) | 6023.86 (5965.22, 6082.50) | 14883.41 (14777.64, 14989.17) |
| Women | Most Affluent | 151.95 (134.53, 169.37) | 286.74 (261.92, 311.55) | 602.05 (562.52, 641.58) | 1275.1 (1212.39, 1337.80) | 2936.87 (2828.25, 3045.48) | 6735.86 (6524.70, 6947.02) | 12731.93 (12328.55, 13135.31) | 27583.5 (26631.05, 28535.95) |
| | Moderate | 120.37 (99.3, 141.44) | 232.11 (200.17, 264.05) | 497.4 (444.23, 550.58) | 1051.35 (970.37, 1132.33) | 2474.07 (2338.15, 2609.99) | 5486.21 (5230.99, 5741.43) | 10322.1 (9842.93, 10801.27) | 22473.22 (21434.62, 23511.83) |
| | Most Deprived | 160.07 (116.00, 204.14) | 303.71 (237.13, 370.3) | 542.13 (443.24, 641.02) | 1009.9 (884.12, 1135.69) | 2526.01 (2328.79, 2723.24) | 5248.32 (4918.08, 5578.56) | 10004.11 (9423.17, 10585.04) | 21800.21 (20605.22, 22995.20) |
| | Total | 175.31 (160.98, 189.65) | 301.32 (281.42, 321.21) | 590.79 (559.83, 621.75) | 1182.56 (1136.13, 1229.00) | 2606.21 (2529.90, 2682.51) | 5670.66 (5529.08, 5812.24) | 10404.69 (10143.34, 10666.03) | 22286.6 (21704.66, 22868.54) |

SES – Socioeconomic status
CI – Confidence Intervals

Considering the model described above, an interaction between age and SES in HF incidence was observed for both sexes: in medium and affluent areas the incidence rates were lower in younger age-groups, and higher in older age-groups, when compared with the most deprived areas (Figure 2 and Table 3). The relative risks (RR) were statistically significantly different from one in the age groups of 75-79, 80-84 and 85+ in affluent municipalities (using deprived municipalities as reference) in both sexes and there are others in the borderline of the significance, such as in women in age group of 50-55 (Table 3).

**Figure 2 – Relative risk of hip fractures, by sex, age group and three classes of socioeconomic status, using the most deprived as reference**

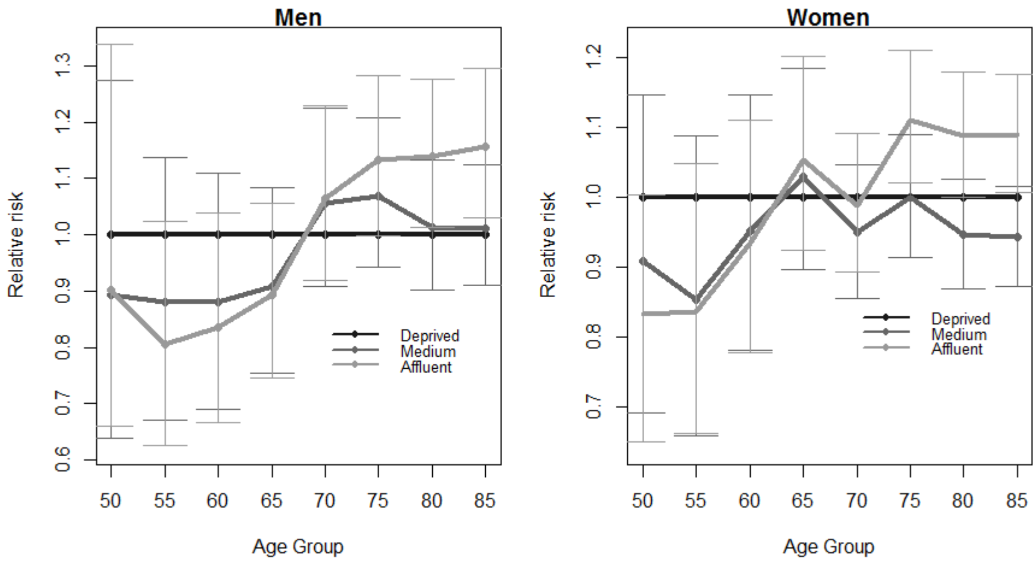


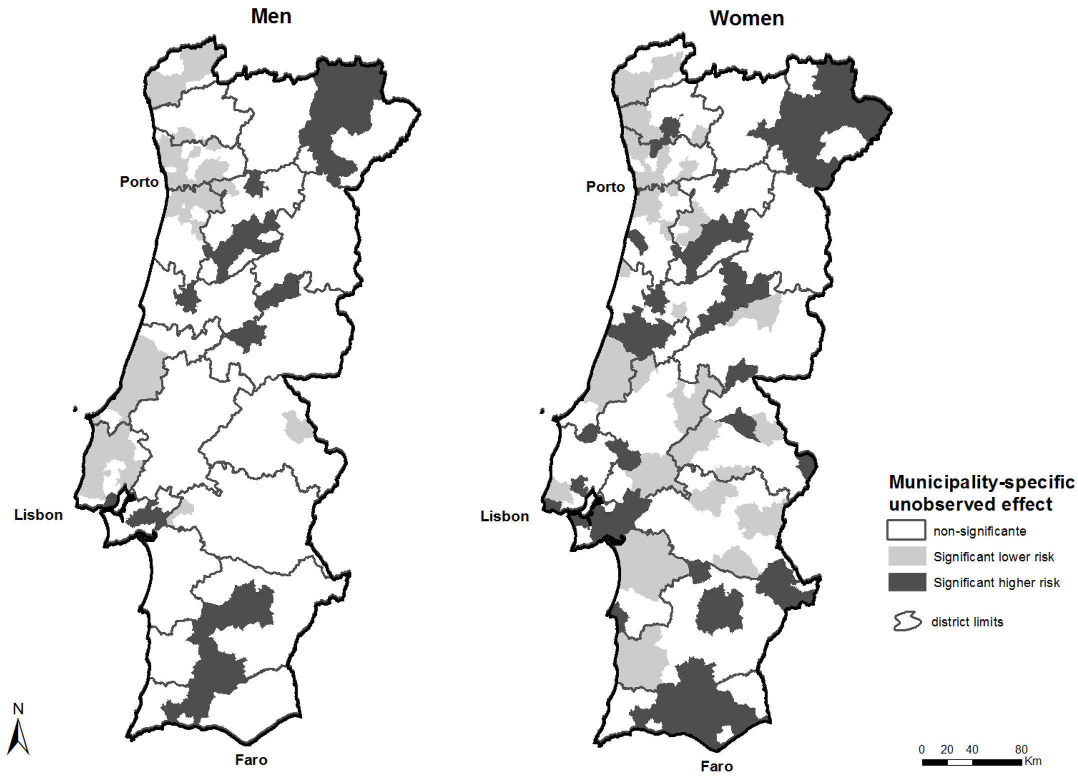
**Table 3 – Relative risk of hip fractures (95%CrI) by sex, age group and three classes of socioeconomic status, using the most deprived as reference**

| | Men | | | Women | | |
|---|---|---|---|---|---|---|
| | RR * (95%CrI) | | | RR * (95%CrI) | | |
| Age Group | Deprived | Medium | Affluent | Deprived | Medium | Affluent |
| 50-54 | Ref | 0.89 (0.64, 1.27) | 0.90 (0.66, 1.34) | Ref | 0.91 (0.69, 1.15) | 0.83 (0.65, 1.00) |
| 55-59 | Ref | 0.88 (0.67, 1.14) | 0.81 (0.63, 1.02) | Ref | 0.85 (0.66, 1.09) | 0.84 (0.66, 1.05) |
| 60-64 | Ref | 0.88 (0.69, 1.11) | 0.84 (0.67, 1.04) | Ref | 0.95 (0.78, 1.15) | 0.93 (0.78, 1.11) |
| 65-69 | Ref | 0.91 (0.76, 1.08) | 0.89 (0.75, 1.06) | Ref | 1.03 (0.90, 1.18) | 1.05 (0.92, 1.20) |
| 70-74 | Ref | 1.06 (0.91, 1.22) | 1.06 (0.92, 1.23) | Ref | 0.95 (0.86, 1.05) | 0.99 (0.89, 1.09) |
| 75-79 | Ref | 1.07 (0.94, 1.21) | 1.13 (1.00, 1.28) | Ref | 1.00 (0.91, 1.09) | 1.11 (1.02, 1.21) |
| 80-84 | Ref | 1.01 (0.90, 1.13) | 1.14 (1.01, 1.28) | Ref | 0.95 (0.87, 1.03) | 1.09 (1.00, 1.18) |
| 85+ | Ref | 1.01 (0.91, 1.12) | 1.16 (1.03, 1.30) | Ref | 0.94 (0.87, 1.02) | 1.09 (1.01, 1.18) |

(*) Adjusted for rural conditions
CrI – Credible Intervals
RR – Relative Risk
Ref – Reference

Figure 3 shows the significant higher and lower RR of HF attributed to unobserved spatial effect. It seems that there are two areas of municipalities with the particularly higher risk of HF (Northeast and the very South). This may be related to unobserved variables and future investigation needs to be performed.

**Figure 3 – Significant higher and lower municipality-specific unobserved effect of hip fractures**




## Discussion

Our study suggests that, at an ecological level, the main effect of the risk of HF is related with the SES of patients' municipality of residence. In both sexes, a higher risk was observed in deprived municipalities and a trend was identified in women: more affluent areas, lower risk; however our results are in the borderline significant or are not statistically significant.

This inverse relation between HF risk and SES observed in our study is in accordance with a set of studies that explored this issue. In Oslo (Norway) [29] a study including population aged 50 years and over found a higher risk of HF in deprived areas compared with more affluent ones; in Geneva (Switzerland) [30] a study also including population aged 50 years and over found a higher risk in low-income regions compared with medium and higher income regions and their results were similar to a study in Sweden [13] including population in all ages. The same direction of this association was found in an Australian study [16], using a private health insurance as a proxy for higher SES and including population aged 65 years and over. In the Trend region (north of England) [7] a study using the Townsend deprivation index as a proxy for SES, found a significant inverse association with the risk of falls; although, no association between HF and deprivation was found [7] and this may be due to the low statistical power of the study [15] or because only individuals aged >74 years were included in the study (the association between SES and HF can be dependent on the age group). In the United States [31], in a community-dwelling of people aged ≥70 years and over there was a non-significant inverse association between HF and income.

Socioeconomic status seems to be also related to bone mineral density - individuals with higher income [32] and higher education [33] had higher BMD when compared with individuals with lower income and education.

The higher risk of HF in individuals living in deprived areas may result from a combination of lifestyle, environmental and social factors: unhealthy lifestyles can lead to higher risk of osteoporosis[2]; inappropriate built environment can lead to higher risk of falls [34]; and lower access to health services can lead to lower access to actions for osteoporosis prevention [35]. Even though in Portugal access to the national health-care system is universal and tendentiously free-of-charge, regions with lower SES can be more isolated, with lower street connections and lack of public transports which may difficult the access to health centers.

The observed increasing trend, at the individual level, of the mean age at admission with the decrease in SES can be due to the age structure of the population since the regions with lower SES have the highest proportion of elderly.

An interaction between SES and age was observed, more accentuated among men: youngest adults living in areas with higher SES had a lower risk of HF compared to those living in lower SES areas and the reverse occurs for the oldest individuals. Few studies have evaluated the age interaction between HF and SES, but results similar to ours were found in Wales and Denmark [15, 18]. The lower risk in the youngest living in more affluent areas may be a result of a cohort effect: higher education in the younger may influence risk behaviors [18]. In Wales, among individuals aged < 75 years an inverse association was observed between HF incidence and deprivation of the region of residence, although the relationship disappears in older age groups (>75 years) [15]. In Denmark, the association between HF risk and income was not significant and a possible reason can be the reduced social inequalities [18]. In Spain, an interaction between age and income was found in the relation between BMD and income: youngest adults (20-39 years-old) had a higher BMD in the more affluent areas compared to the more deprived areas and a reverse relation was observed in the older ages [32]. A U-shape relation between BMD and SES was also found in an Australian study (women, over 18 years) - individuals living in the extreme categories of SES had lower Bone Mineral Density (BMD) [36]

For women, the age interaction with SES was not so clear: older women from areas in the medium SES had lower risk compared to women from lower SES areas and we need further studies to understand if this pattern is related to risk factors such as obesity, physical activity, occupational work, etc; risk for women in the age group 70-74 years was similar in the three SES areas and this may be due to the fact that in Portugal the health guidelines for osteoporosis prevention are mainly focusing on women between 65-74 ages.

A limitation of our study is the absence of individual data for SES and for previous places of patient´s residence; therefore, conclusions need to be taken with caution. The age interaction on the relative risk between HF and SES could be a consequence of changes in place of residence of the elderly. Older and frail individuals, living in more isolated and deprived municipalities, may have moved to more affluent municipalities to live with or close the caregivers. However, other studies tested this hypothesis and non-significant differences were found in the mean change of SES on moving to another place [15]. Our study refers to a period of eleven years at a nationwide level and it is unlikely that the eventual migration within the country would affect a high percentage of the elders.

The strength of our study is that we used longitudinal data from nationwide registers and a rigorous study design that minimize the risk of selection and information bias. Besides, we used powerful statistical analysis to measure the association between socioeconomic status and hip fractures. The use of socioeconomic status per municipality was helpful in recognizing areas of higher risk of HF and can help in the design of public health intervention programs.

**Conclusion:**

Ecological studies can help in the identification of areas/population groups at higher risk of hip fractures. This area-level study suggests a general pattern, the more deprived municipalities presented a higher risk of hip fracture, and an interaction between age group and socioeconomic status of the municipality of residence in the risk of hip fracture; the association between hip fractures incidence and socioeconomic status was inverse in younger ages (lower risk in more affluent areas) and direct in older ages (higher risk in more affluent areas). These results may help decision-makers to better understand the epidemiology of hip fractures and better direct the implementation of political decisions.

**References**

1. Morrison A, Fan T, Sen SS, Weisenfluh L. Epidemiology of falls and osteoporotic fractures: a systematic review. ClinicoEconomics and outcomes research : CEOR. 2013;5:9-18. Epub 2013/01/10.

2. NIH Consensus Development Panel on Osteoporosis Prevention, Diagnosis, and Therapy, March 7-29, 2000: highlights of the conference. South Med J. 2001;94(6):569-73. Epub 2001/07/07.

3. Ivergård M, Svedbom A, Hernlund E, Compston J, Cooper C, Stenmark J, et al. Epidemiology and Economic Burden of Osteoporosis in Portugal. A report prepared in collaboration with the International Osteoporosis Foundation (IOF) and the European Federation of Pharmaceutical Industry Associations (EFPIA). Archives of osteoporosis. 2013;8:137 (1-2):pag 167.

4. Bischoff HA, Stahelin HB, Dick W, Akos R, Knecht M, Salis C, et al. Effects of vitamin D and calcium supplementation on falls: a randomized controlled trial. J Bone Miner Res. 2003;18(2):343-51. Epub 2003/02/06.

5. Kanis JA, Pitt FA. Epidemiology of osteoporosis. Bone. 1992;13 Suppl 1:S7-15.

6. Pina MF, Alves SM, Barbosa M, Barros H. Hip fractures cluster in space: an epidemiological analysis in Portugal. Osteoporos Int. 2008.

7. West J, Hippisley-Cox J, Coupland CA, Price GM, Groom LM, Kendrick D, et al. Do rates of hospital admission for falls and hip fracture in elderly people vary by socio-economic status? Public Health. 2004;118(8):576-81. Epub 2004/11/09.

8. Kanis JA, Borgstrom F, Compston J, Dreinhofer K, Nolte E, Jonsson L, et al. SCOPE: a scorecard for osteoporosis in Europe. Archives of osteoporosis. 2013;8(1-2):144. Epub 2013/09/14.

9. Benetos IS, Babis GC, Zoubos AB, Benetou V, Soucacos PN. Factors affecting the risk of hip fractures. Injury. 2007;38(7):735-44. Epub 2007/02/20.

10. Korpelainen R, Korpelainen J, Heikkinen J, Vaananen K, Keinanen-Kiukaanniemi S. Lifelong risk factors for osteoporosis and fractures in elderly women with low body mass index--a population-based study. Bone. 2006;39(2):385-91. Epub 2006/03/15.

11. Farahmand BY, Persson PG, Michaelsson K, Baron JA, Parker MG, Ljunghall S, et al. Socioeconomic status, marital status and hip fracture risk: a population-based case-control study. Osteoporos Int. 2000;11(9):803-8. Epub 2001/01/10.

12. Icks A, Haastert B, Wildner M, Becker C, Rapp K, Dragano N, et al. Hip fractures and area level socioeconomic conditions: a population-based study. BMC Public Health. 2009;9:114. Epub 2009/04/29.

13. Farahmand BY, Persson PG, Michaelsson K, Baron JA, Parker MG, Ljunghall S. Socioeconomic status, marital status and hip fracture risk: a population-based case-control study. Osteoporos Int. 2000;11(9):803-8. Epub 2001/01/10.

14. Suen LK. Occupation and risk of hip fracture. J Public Health Med. 1998;20(4):428-33. Epub 1999/01/29.

15. Jones S, Johansen A, Brennan J, Butler J, Lyons RA. The effect of socioeconomic deprivation on fracture incidence in the United Kingdom. Osteoporos Int. 2004;15(7):520-4. Epub 2004/04/02.

16. Peel NM, McClure RJ, Hendrikz JK. Psychosocial factors associated with fall-related hip fractures. Age Ageing. 2007;36(2):145-51. Epub 2007/01/30.

17. Brennan SL, Pasco JA, Urquhart DM, Oldenburg B, Hanna F, Wluka AE. The association between socioeconomic status and osteoporotic fracture in population-based adults: a systematic review. Osteoporos Int. 2009;20(9):1487-97. Epub 2008/12/25.

18. Vestergaard P, Rejnmark L, Mosekilde L. Socioeconomic aspects of fractures within universal public healthcare: a nationwide case-control study from Denmark. Scandinavian journal of public health. 2006;34(4):371-7. Epub 2006/07/25.

19. Reimers A, Laflamme L. Hip fractures among the elderly: personal and contextual social factors that matter. J Trauma. 2007;62(2):365-9. Epub 2007/02/14.

20. INE. *Instituto Nacional de Estatística*; [cited 2012]; Available from: www.ine.pt.

21. OECD. Divided we stand: why inequality keeps rising. An Overview of Growing Income Inequalities in OECD Countries: Main Findings. 2011; Available from: http://www.oecd.org/social/inequality.htm.

22. Barros PP, Machado SR, Simoes Jde A. Portugal. Health system review. Health systems in transition. 2011;13(4):1-156. Epub 2012/01/10.

23. ACSS. Auditoria da codificação clínica [Clinical codification Audits]. 2011 Available from: http://portalcodgdh.min-saude.pt/index.php/Auditoria_da_codificação_cl%C3%ADnica.

24. Moreira J. Fracturas Osteoporóticas do Colo do Fémur em Portugal e seus Determinantes Socioeconómicos. Porto: Faculdade de Engenharia da Universidade do Porto.; 2008.

25. Chevalley T, Herrmann FR, Delmi M, Stern R, Hoffmeyer P, Rapin CH, et al. Evaluation of the age-adjusted incidence of hip fractures between urban and rural areas: the difference is not related to the prevalence of institutions for the elderly. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA. 2002;13(2):113-8. Epub 2002/03/22.

26. Banerjee S, Carlin BP, Gelfand AE. Hierarchical modeling and analysis for spatial data. In: Hall/CRC Ca, editor.2004.

27. R Core Team. R: A language and environment for statistical computing. R Foundation for Statistical Computing. Vienna, Austria2012.

28. Spiegelhalter D, Thomas A, Best N, Lunn D. WinBUGS User Manual (Version 1.4). 2003 January 2003. Report No.

29. Kaastad TS, Meyer HE, Falch JA. Incidence of hip fracture in Oslo, Norway: differences within the city. Bone. 1998;22(2):175-8. Epub 1998/02/26.

30. Guilley E, Herrmann F, Rapin CH, Hoffmeyer P, Rizzoli R, Chevalley T. Socioeconomic and living conditions are determinants of hip fracture incidence and age occurrence among community-dwelling elderly. Osteoporos Int. 2011;22(2):647-53. Epub 2010/05/19.

31. Wilson RT, Chase GA, Chrischilles EA, Wallace RB. Hip fracture risk among community-dwelling elderly people in the United States: a prospective study of physical, cognitive, and socioeconomic indicators. Am J Public Health. 2006;96(7):1210-8. Epub 2006/06/01.

32. del Rio Barquero L, Romera Baures M, Pavia Segura J, Setoain Quinquer J, Serra Majem L, Garces Ruiz P, et al. Bone mineral density in two different socio-economic population groups. Bone Miner. 1992;18(2):159-68. Epub 1992/08/01.

33. Varenna M, Binelli L, Zucchi F, Ghiringhelli D, Gallazzi M, Sinigaglia L. Prevalence of osteoporosis by educational level in a cohort of postmenopausal women. Osteoporos Int. 1999;9(3):236-41. Epub 1999/08/18.

34. Rapiti E, Fioretta G, Schaffar R, Neyroud-Caspar I, Verkooijen HM, Schmidlin F, et al. Impact of socioeconomic status on prostate cancer diagnosis, treatment, and prognosis. Cancer. 2009;115(23):5556-65. Epub 2009/09/30.

35. Neuner JM, Zhang X, Sparapani R, Laud PW, Nattinger AB. Racial and socioeconomic disparities in bone density testing before and after hip fracture. J Gen Intern Med. 2007;22(9):1239-45. Epub 2007/06/28.

36. Brennan SL, Henry MJ, Wluka AE, Nicholson GC, Kotowicz MA, Williams JW, et al. BMD in population-based adult women is associated with socioeconomic status. J Bone Miner Res. 2009;24(5):809-15. Epub 2008/12/31.

## 3.3 Marked socioeconomic inequalities in hip fractures incidence rates during the bone and joint decade (2000-2010): age and sex temporal trends in a population-based study

Article published in J Epidemiol Community Health

DOI: 10.1136/jech-2015-206508.

Date 2016 Jan 19

# MARKED SOCIOECONOMIC INEQUALITIES IN HIP FRACTURES INCIDENCE RATES DURING THE BONE AND JOINT DECADE (2000-2010): AGE AND SEX TEMPORAL TRENDS IN A POPULATION-BASED STUDY

**Oliveira CM, Alves SM, Pina MF**

**Carla Maria Oliveira**

i3S - Instituto de Investigação e Inovação em Saúde, Universidade do Porto, Portugal;

INEB - Instituto de Engenharia Biomédica, Universidade do Porto, Rua do Campo Alegre, 823, 4150-180 Porto, Portugal;

ESTSP/IPP - Escola Superior de Tecnologia da Saúde do Porto, Instituto Politécnico do Porto, Rua Valente Perfeito, 322, 4400-330 Vila Nova de Gaia, Portugal;

FMUP - Faculdade de Medicina da Universidade do Porto, Al. Prof. Hernâni Monteiro, 4200 - 319 Porto, Portugal

ISPUP - Instituto de Saúde Pública da Universidade do Porto, Rua das Taipas 135, 4050-600, Porto, Portugal

coliveir@ineb.up.pt

**Sandra Maria Alves**

i3S - Instituto de Investigação e Inovação em Saúde, Universidade do Porto, Portugal;

INEB - Instituto de Engenharia Biomédica, Universidade do Porto, Rua do Campo Alegre, 823, 4150-180 Porto, Portugal;

ESTSP/IPP - Escola Superior de Tecnologia da Saúde do Porto, Instituto Politécnico do Porto, Rua Valente Perfeito, 322, 4400-330 Vila Nova de Gaia, Portugal;

smfa@ineb.up.pt

**Maria Fátima Pina**

ICICT/FIOCRUZ - Instituto de Comunicação e Informação em Saúde/Fundação Oswaldo Cruz, Av. Brasil 4365, Av. Brasil, 4.365 - Pavilhão Haity Moussatché - Manguinhos, Rio de Janeiro, CEP: 21040-900,

i3S - Instituto de Investigação e Inovação em Saúde, Universidade do Porto, Portugal;

INEB - Instituto de Engenharia Biomédica, Universidade do Porto, Rua do Campo Alegre, 823, 4150-180 Porto, Portugal;

FMUP - Faculdade de Medicina da Universidade do Porto, Al. Prof. Hernâni Monteiro, 4200 - 319 Porto, Portugal

CARTO-FEN/UERJ - Departamento de Engenharia Cartográfica, Faculdade de Engenharia da Universidade do Estado do Rio de Janeiro. Rua São Francisco Xavier, 524/4ºandar, Maracanã, CEP:20550-900, Rio de Janeiro – RJ, Brazil.

fatima.pina@icict.fiocruz.br

**Corresponding author**: C M Oliveira; coliveir@ineb.up.pt; phone: +351 226074900 ; Fax: +351 226094567; INEB, Instituto de Engenharia Biomédica, Universidade do Porto, Rua do Campo Alegre, 823, 4150-180 Porto, Portugal

**Abstract**

**Background**: Socioeconomic factors may influence changes in hip fracture (HF) incidence over time. We analyzed HF temporal trends during the bone and joint decade in Portugal (BJD-Portugal), 2000-2010, by regional socioeconomic status (SES), sex and age.

**Methods**: From the National Hospital Discharge Database we selected registers of patients aged 50+ with HF (ICD9-CM) caused by traumas of low/moderate energy. Annual time series of age-specific incidence rates were calculated by sex and regional SES (deprived, medium, affluent). Generalized additive models were fitted to identify shape/turning points in temporal trends.

**Results**: We selected 96,905 HF (77.3% in women). Women are older than men at admission (81.2±8.5 vs 78.2±10.1 years-old, $p<0.001$). For women 65-79 years: a continuously decreasing trend (1.7%/year) only in affluent and increasing trends (3.3-3.4%/year) after 2006/2007 in medium and deprived was observed. For men, trends are stable or increase in almost all age/SES groups (only two decreasing periods). For the oldest women, all SES present similar trends: turning points around 2003 (initiating decreasing periods: 1.8-2.9%/year) and around 2007 (initiating increasing periods: 3.7-3.3%/year).

**Conclusion**: There are SES-sex-age inequalities in temporal trends during BJD-Portugal: marked SES inequalities among women 65-79 years-old (a persistent, decreasing trend only in the affluent) vanish among the oldest women; the same was not observed in men, for them there were almost no declining periods; women ≥80 years-old, present increasing trends around 2007, as in most of deprived/age/sex groups. Despite some successful periods of decreasing trends, incidence rates did not improve overall, in almost all age groups and both sexes.

**Keywords:** Hip fractures, incidence rates, regional socioeconomic status, temporal trends, time series analysis, Bone and Joint Decade

**What is already known on this subject**

‣ An inverse association between socioeconomic status and osteoporosis or HF (not all consistent) has been generally reported in cross-sectional studies, probably due to unhealthy behaviors such as poor diet, inadequate exercise or harmful occupational environments, which are more frequent in deprived populations.

**What this study adds**

‣ Even though temporal trends have been widely explored, studies reporting differences in temporal trends by SES are sparse. ‣ Our results are surprising and may contribute to the discussion and reflection of current interventions to reduce HF. ‣ Incidence rates of HF has changed over time in different regional SES per age group and sex. ‣ Women 65-79 years old, who are frequently the preferential target population for osteoporosis and HF prevention, show the strongest SES inequalities: only those from affluent regions have a continuous decreasing trend, whereas those from deprived regions have no decreasing and, on the contrary, have an increasing trend since 2006/2007. ‣ Surprisingly, the SES inequalities vanish among the oldest women (≥ 80 years) – all of them, regardless of the regional SES, show increasing trends after 2006/2007 similar to what occurs in both sexes and all ages from deprived regions (although not all are significant). ‣ For men, overall temporal trends are stable, which could reflect the lack of attention given to bone health in men.

## Introduction

Hip fractures (HF), one of the most preventable causes of disabilities in the elderly[1], are a major public health problem because of their association with high morbidity and mortality rates and their economic impact on individuals and societies[2]. Therefore, hip fractures were included among the disorders prioritized by the Bone and Joint Decade (BJD) initiative. This initiative resulted from the concern of healthcare professionals about the significant impact of these disorders on society, the healthcare system, and individuals. Launched in 2000 and running until 2010, its primary aim was to promote advances in the knowledge, diagnosis and treatment of musculoskeletal disorders. The goal of the BJD was: "to improve the health-related quality of life for people with musculoskeletal disorders throughout the world by raising awareness and promoting positive actions to combat the suffering and costs to society associated with musculoskeletal disorders"[3]. More than sixty countries, including Portugal, signed this initiative[4] and made commitments to reduce HF incidence. The BJD was renewed for the decade 2010-2020 as a global alliance for musculoskeletal health[5, 6].

It is known that socioeconomic factors are determinant for disparities in health behaviors, incidence of diseases and mortality[7]; an inverse association between several health outcomes and socioeconomic status (SES) has been reported: deprived SES individuals, or regions, present higher morbidity and mortality rates in general[7, 8]. The inverse association between SES and osteoporosis or HF reported in the literature (not all of which are consistent)[9, 10] might be partially explained by unhealthy behaviors such as poor diet, inadequate exercise or harmful occupational environments, which are more frequent in deprived populations[11, 12].

Overall, strong inequalities in temporal trends of HF incidence have been described between and within countries[13, 14]. Several studies have reported increasing trends in HF incidence until the beginning of the last decade (around 2000) and increasing longevity – combined with socioeconomic, demographic and environmental risk factors – have been pointed out as a possible explanation[15, 16]. However, during the past decade (after 2000), stabilization or decreasing in HF incidence by sex and age groups have also been described in most western countries and Oceania[17-21] and might be the result of prevention strategies, either medical (pharmaceutical treatment for osteoporosis) or non-medical (fall prevention)[22, 23]. Even though temporal trends have been widely explored, studies reporting differences in temporal trends by SES are sparse and, to our knowledge, there are no studies reporting how HF incidence rates have changed over time in different regional SES per age group.

To overcome the gap in the literature, we conducted a population-based study in Portugal with the aim to analyze the temporal trends of HF incidence rates during the Bone and Joint Decade (2000-2010), by sex and age group according to municipality SES regions.

## Material and Methods

### Study area

The study area is Continental Portugal - we excluded from the analysis the two autonomous regions, the archipelagos of Azores and Madeira (5% of the Portuguese population) because there were no available data for these regions. In 2010, there were 10,057,99 inhabitants distributed heterogeneously throughout 278 municipalities, with a median of 15,741 (interquartile range (IQR) 7,371 – 39,356) inhabitants per municipality. Portugal is one of the highest aged countries in Europe-27: in 2010 it was the fifth country in the ranking of the highest percentage of persons aged 65 and over[24], with an ageing index of 120 elderly (≥65 years-old) per 100 youths (≤14 years-old) and 37.7% of the population over 50 years old (INE - Statistics Portugal[25]).

### Data

We used data from the National Hospital Discharge Register (NHDR), mandatory for all Portuguese public hospitals since 1997. The quality of the NHDR is assessed regularly by internal and external auditors. It is done initially in the hospital by internal auditors and after by external auditors from the Central Administration of the National System (ACSS). Internal and external auditors are mandatory medical coders trained by the ACSS. The evaluation of quality is performed systematically in order to determine whether the encoding and the resulting grouping Diagnosis Related Groups (DRG) comply with the coding rules, and these are effectively implemented in order to achieve the objectives of the System Patient Classification in DRG[26]. More detail about the NHDR can be found elsewhere[26]; briefly: each register corresponds to one episode of hospital admission and contains variables such as sex, age, cause of admission (main and up to 19 secondary causes) and diagnosis (main and up to 19 secondary diagnoses) coded according to the International Classification of Diseases, version 9 - Clinical Modification (ICD9-CM), the municipality of patient's residence, and the date of admission, among others. For confidentiality reasons, data was available without information that would allow identification of the patient, such as name, code, address or ID number. During the study period, access to the Portuguese health-care system (health centers and hospital consultations and internments) was based on principles of universality, integrality, and equity and were mostly free-of-charge: contributions were based upon citizens socioeconomic conditions [27] and almost the totality of patients with HF were treated in public hospitals. Therefore, data of HF hospital admissions from the NHDR can be seen as a proxy of HF incidence in Portugal.

We selected all hospital discharge registers of patients hospitalized from 1 January 2000 to 31 December 2010, aged 50 years and over, with a diagnosis of HF (main, second or third diagnosis) (ICD9-CM codes 820.x) with the main cause being trauma of low/moderate energy (main cause of admission) (ICD9-CM codes E849.0, E849.7 and E880-E888). We excluded readmissions for aftercare (ICD9-CM codes 996.4 and V54.x) and pathological fractures (ICD9-CM codes 170.x and 171.x) if registered in one of the twenty. Procedure codes were also taken into consideration to detect and exclude cases with a misclassification readmission on the diagnosis field. Cases with a length of stay inferior to 5 days and transferred to another hospital without surgery were also excluded (the first hospitalization could only be for stabilization of the patient). Counts of HF were stratified by the municipality of patient's residence, admission year, sex and three age groups (50-64, 65-79, 80+).

For age-specific incidence rates, we used population counts per municipality from the 2001 Census and from the official estimates for all the other years[25], stratified in the same groups of hospital admission data.

Each municipality was classified, according to SES, as deprived, medium or affluent; analyses were conducted according to the region's SES. The methods for the classification of municipalities according to SES can be found in detail elsewhere[28]. In brief, we reduced to four principal components (PC) a set of 30 socioeconomic and demographic variables related to building, households, families, and individuals from the 2001 census based on the Kaiser Criterion (eigenvalues ≥1) which retained 75.8% of the total variability. A varimax rotation was then applied to the four PC for interpretation and to reduce the dimensionality of the data at a set of uncorrelated variables that account for much of the original data. After, we conducted a hierarchical cluster analysis based on Ward's method to identify homogenous areas. Municipalities were then aggregated in three clusters of SES that were empirically interpreted as follows: the affluent SES comprises municipalities with younger population, higher educational level, higher percentage of employed individuals, good housing conditions (plumbing, heating, shower and bathroom facilities); compared to the affluent areas, the medium SES comprises municipalities with older populations, higher illiteracy rates, a lower gross domestic product (GDP) per capita and a higher percentage of individuals employed in agricultural, forestry and industry; compared to the affluent and medium areas, the deprived SES comprises municipalities with the highest percentage of elderly, the highest illiteracy rate, the highest rate of people living alone, the lowest level of education, the lowest GDP per capita, the highest percentage of individuals with rural activities, the highest percentage of houses with no running water, no shower and bathroom facilities, and the highest percentage of individuals receiving unemployment benefits[29]. The population (≥50 years-old) significantly differs by SES group ($p<0.001$), with the median: 1,607 (IQR 1,207 – 2,402) in the deprived SES cluster; 3,473 inhabitants (IQR 2,386 – 6,285) in the medium SES cluster and 7,426 inhabitants (IQR 3,453 – 12,706) in the affluent SES cluster.

**Statistical analysis**

We computed annual time series of the age-specific incidence rates, expressed as admissions per 100,000 persons-year (PY) stratified by sex and regions SES. The age-specific incidence rates were calculated by dividing the total admissions by the total population, per year, sex, SES and age groups 50-64, 65-79 and 80+ (the total admissions and population for each year, SES, sex and age group can be seen in supplementary table 1).

Generalized additive models, that incorporate a non-parametric component, s(.), estimated using spline functions (smoothers, useful in revealing possible nonlinearities in the effect of the predictors), were fitted to identify the shape and turning points where the temporal trend changes significantly in magnitude and/or direction during the study period. Annual (and period) absolute and relative changes over time were quantified between turning points (or between turning points and extremes, in the case of the first and last period) of the time series (more detail can be seen in supplementary methods 1).

We assumed that the number of HF ($NFrat_t$) in a specific year $t$ follows a Poisson distribution with mean $\lambda_t = NPop_t \varrho_t$, where $NPop_t$ is the population in year $t$ and $\varrho_t$ is the incidence rate of HF per unit of population in year $t$ (or follows a negative binomial distribution with the scale parameter $\theta$ to account for overdispersion).

For each sex, age group and regional SES, the parameters of interest were estimated by the following model:

$NFrat_t \sim Pois(\lambda_t)$ or $NFrat_t \sim NegBin(\lambda_t, \theta)$

$$log(\lambda_t) = log(NPop_t) + log(\varrho_t) = log(NPop_t) + \beta_0 + s\left(Year^{(t)}\right)$$

The statistical analysis was performed using the packages mgcv and MASS of the statistical software R version 2.14.1 (Project for Statistical Computing).

**Results**

There were 98,186 admissions, of patients aged 50 years and over, with a diagnosis of HF caused by traumas of low/moderate energy in Continental Portugal between 2000 and 2010. From those, we excluded 585 due to missing data in the municipality of the patient's residence and 696 due to readmissions for aftercare; our final sample includes 96,905 fractures (77.3% in women). On average, women are older than men at admission, with a mean age ± standard deviation of 81.2±8.5 versus 78.2±10.1 years-old, $p<0.001$.

Figure 1 shows the temporal trends of age-specific incidence rates (estimated rates for each year, SES, sex and age group are presented in supplementary table 2) and Table 1 presents the estimated absolute and relative changes in the trends of age-specific incidence rates per 100,000 PY (95% confidence intervals - CI), by regional SES and age groups in women. Only among the group of oldest women are there no differences in the trends of HF due to the region's SES – for this group, we observed a decreasing trend from 2002/2004 to 2006/2007, followed by an increasing trend until the end of the study period. In the other age groups, there are marked SES differences in trends: for younger women (50-64 years-old) there are no changes over time, except in the affluent regions where there are slight decreasing trends (1.9% HF per year) from 2000 to 2007. For women aged 65-79 years: in the affluent regions, there is a continuously decreasing trend in the overall period (1.7% HF per year) while for the medium regions, there is an abrupt decreasing trend (4.7% HF per year) for a short period (2004 to 2007) followed by an increasing trend (3.4% HF per year). On the other hand, in the deprived regions only an increasing trend was observed (2006 to 2010) with an increment of 3.3% HF per year.

**Figure 1 – Estimated temporal trends (2000-2010) of age-specific incidence rates of hip fracture, per 100,000 persons-year (95% confidence interval) by socioeconomic status regions and age groups in women**

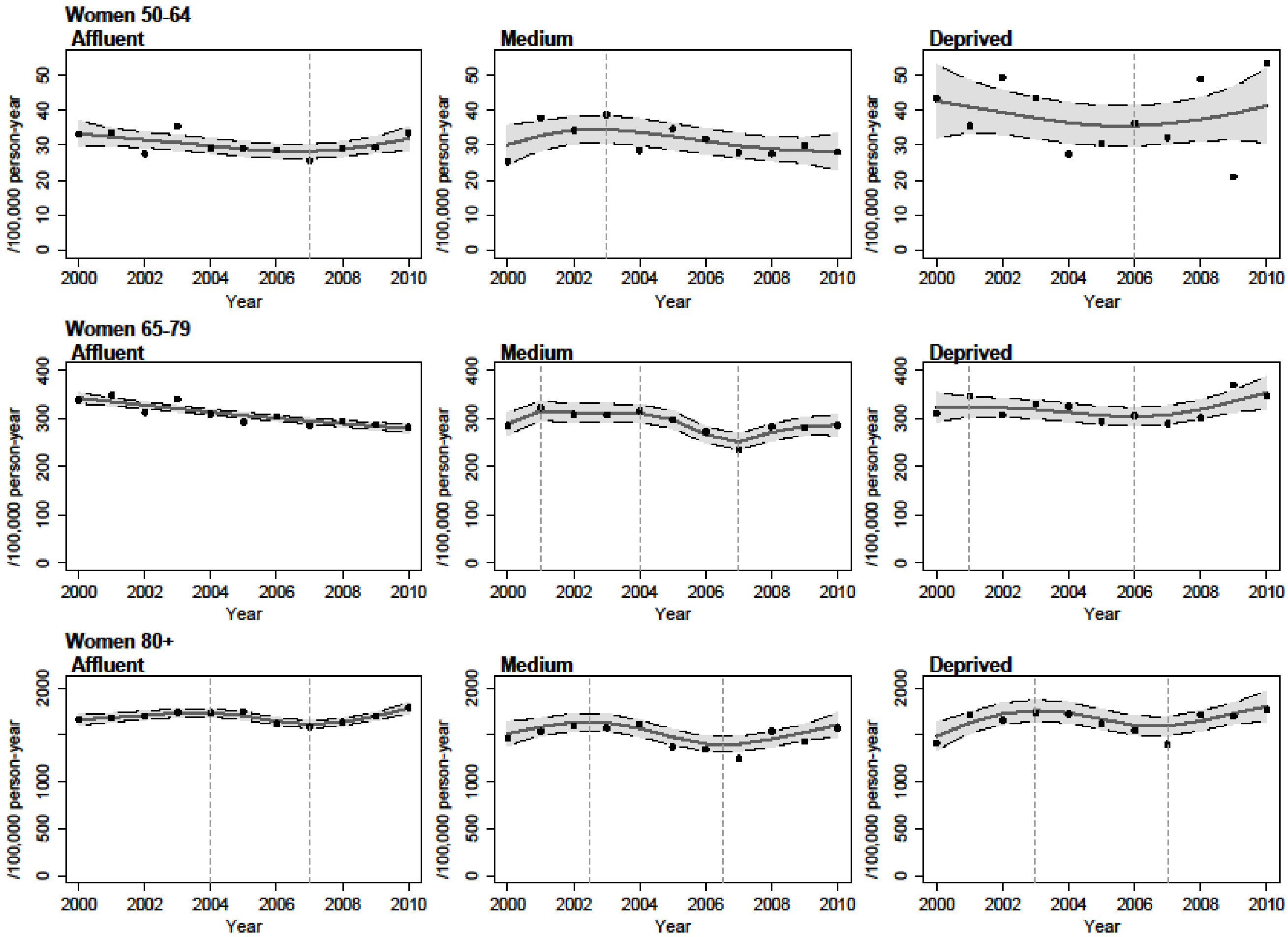


**Table 1 – Estimated absolute and relative changes in temporal trends (2000-2010) of age-specific incidence rates of hip fracture, per 100,000 persons-year, (95% confidence interval) by socioeconomic status regions and age groups in women**

| AgGr | SES | Period | AIR | AAC | PAC | ARC | PRC |
|---|---|---|---|---|---|---|---|
| AgGr50-64 | Affluent | 2000-2007* | 33.2 (29.5, 36.9) | -0.6 (-1.2, -0.1) | -5.1 (-9.2, -0.9) | -1.9 (-3.2, -0.4) | -15.3 (-25.6, -3.2) |
| | | 2007-2010 | 28.2 (26.2, 30.2) | 0.9 (0.0, 1.8) | 3.7 (-0.1, 7.4) | 3.2 (-0.1, 7.0) | 12.8 (-0.2, 28) |
| | Medium | 2000-2003 | 30.1 (24.4, 35.7) | 1.2 (-0.7, 2.8) | 4.8 (-2.9, 11.1) | 4 (-2.1, 11.1) | 15.9 (-8.4, 44.5) |
| | | 2003-2010 | 34.5 (30.6, 38.5) | -0.8 (-1.6, 0.0) | -6.4 (-13.1, 0.1) | -2.3 (-4.6, 0) | -18.5 (-36.4, 0.2) |
| | Deprived | 2000-2007 | 42.6 (32.1, 53.0) | -0.9 (-2.6, 0.8) | -6.6 (-18, 5.5) | -2.2 (-5.1, 2.5) | -15.5 (-35.8, 17.3) |
| | | 2007-2010 | 36.1 (30.3, 42.0) | 1.1 (-1.4, 3.6) | 5.7 (-6.8, 18.1) | 3.2 (-3.5, 10.9) | 15.8 (-17.4, 54.6) |
| AgGr65-79 | Affluent | 2000-2010* | 342.6 (331.5, 353.7) | -5.8 (-7.1, -4.5) | -63.3 (-78, -49.3) | -1.7 (-2.0, -1.3) | -18.5 (-22.2, -14.8) |
| | Medium | 2000-2001 | 289.0 (266.2, 311.8) | 13.4 (-1.2, 28.2) | 26.7 (-2.5, 56.5) | 4.6 (-0.4, 10.6) | 9.2 (-0.8, 21.1) |
| | | 2001-2004 | 315.3 (295.1, 335.5) | -1.1 (-7.8, 5.9) | -4.5 (-31.1, 23.7) | -0.4 (-2.4, 2.0) | -1.4 (-9.4, 7.8) |
| | | 2004-2007* | 310.8 (292.1, 329.5) | -14.7 (-21.1, -8.6) | -58.8 (-84.2, -34.5) | -4.7 (-6.5, -2.9) | -18.9 (-26.1, -11.7) |
| | | 2007-2010* | 251.7 (235.2, 268.1) | 8.5 (2.2, 15.2) | 34.1 (8.9, 61) | 3.4 (0.9, 6.3) | 13.5 (3.5, 25.2) |
| | Deprived | 2000-2001 | 323.3 (293.1, 353.6) | 0.5 (-17.3, 19.4) | 0.9 (-34.5, 38.8) | 0.1 (-4.9, 6.5) | 0.3 (-9.8, 13) |
| | | 2001-2006 | 324.4 (303.2, 345.6) | -3.4 (-7.9, 0.7) | -20.6 (-47.5, 4.1) | -1.1 (-2.4, 0.2) | -6.3 (-14.1, 1.3) |
| | | 2006-2010* | 303.8 (284.7, 322.9) | 10.0 (2.3, 17.3) | 49.8 (11.4, 86.4) | 3.3 (0.7, 6.0) | 16.4 (3.6, 29.9) |
| AgGr80mais | Affluent | 2000-2004 | 1663.2 (1599.7, 1726.8) | 14.5 (-0.6, 29.9) | 72.5 (-3.1, 149.5) | 0.9 (0.0, 1.8) | 4.4 (-0.2, 9.2) |
| | | 2004-2007* | 1737.0 (1693.1, 1780.9) | -31.5 (-45.9, -16.5) | -126 (-183.5, -66.1) | -1.8 (-2.6, -1.0) | -7.2 (-10.4, -3.8) |
| | | 2007-2010* | 1611.4 (1571.3, 1651.6) | 43.1 (26.2, 59.7) | 172.2 (104.8, 238.7) | 2.7 (1.6, 3.8) | 10.7 (6.4, 15.1) |
| | Medium | 2001-2002 | 1514.8 (1385.9, 1643.8) | 34.4 (-10.7, 76.9) | 120.6 (-37.4, 269.2) | 2.3 (-0.7, 5.4) | 7.9 (-2.3, 18.9) |
| | | 2002-2006* | 1634.6 (1539.9, 1729.3) | -46.7 (-70.4, -20.9) | -233.6 (-352.2, -104.7) | -2.9 (-4.2, -1.3) | -14.3 (-20.9, -6.7) |
| | | 2006-2010* | 1403.8 (1324.1, 1483.4) | 45.1 (13.1, 81.8) | 203.2 (58.8, 368.2) | 3.2 (0.9, 6.1) | 14.5 (4, 27.2) |
| | Deprived | 2000-2003* | 1486.2 (1337.4, 1635.0) | 68.9 (22.2, 115) | 275.8 (88.9, 460.0) | 4.7 (1.4, 8.5) | 18.6 (5.6, 33.8) |
| | | 2003-2007* | 1759.8 (1646.0, 1873.7) | -34.1 (-62.0, -3.6) | -170.6 (-309.9, -18.0) | -1.9 (-3.4, -0.2) | -9.7 (-16.8, -1.1) |
| | | 2007-2010* | 1591.8 (1490.0, 1693.7) | 52.1 (9.1, 98.6) | 208.4 (36.6, 394.4) | 3.3 (0.6, 6.4) | 13.1 (2.2, 25.4) |

AgGr – Age Group, SES – Regional socioeconomic status, AIR – age-specific incidence rates, per 100,000 persons-year, in the beginning of the period, AAC – Annual absolute change, per 100,000 persons-year, PAC – Period absolute change, per 100,000 persons-year, ARC – Annual relative change (%), PRC – Period relative change (%), * $p<0.05$ for temporal trend (significant change)

Similar analyses were conducted for men and the results are presented in Figure 2 and Table 2. In general, men present fewer differences in the trends compared to women. In younger men (50-64 years-old), no significant changes in the trends are observed. In the 65-79 year-old age group, the affluent regions present a decrease of 1.8% HF per year between 2001 and 2007; on the contrary, the deprived regions have an annual increase of 4.4% HF per year, from 2004 to 2010. For the oldest men (≥80 years-old), a similar pattern was observed in affluent and deprived regions with a stable period followed by an increasing tendency (2006-2010), significant only in affluent regions (an increment of 1.6% HF per year). Contrary to the other regional SES, the medium regions present a decreasing trend from 2003 to 2007 (2.3% HF per year).

**Figure 2 – Estimated temporal trends (2000-2010) of age-specific incidence rates of hip fracture, per 100,000 persons-year (95% confidence interval) by socioeconomic status regions and age groups in men**

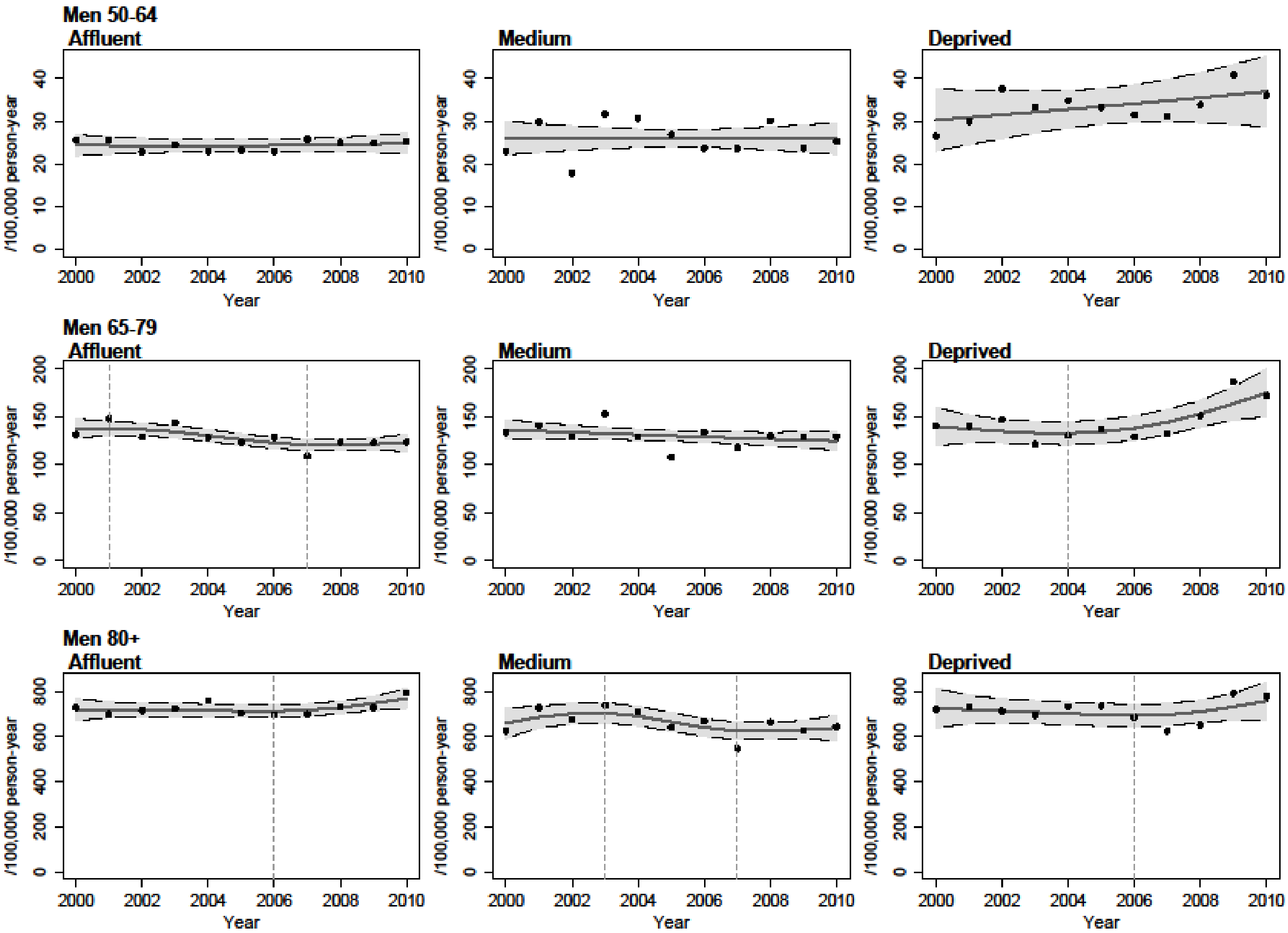


**Table 2 – Estimated absolute and relative changes in temporal trends (2000-2010) of age-specific incidence rates of hip fracture, per 100,000 persons-year, (95% confidence interval) by socioeconomic status regions and age groups in men**

| AgGr | SES | Period | AIR | AAC | PAC | ARC | PRC |
|---|---|---|---|---|---|---|---|
| AgGr50-64 | Affluent | 2000-2010 | 24.4 (21.9, 26.9) | 0.0 (-0.3, 0.3) | 0.5 (-3.3, 3.8) | 0.2 (-1.1, 1.5) | 2.2 (-12.5, 16.4) |
| | Medium | 2000-2010 | 26.0 (22.1, 30.0) | 0.0 (-0.5, 0.5) | -0.1 (-5.2, 5.1) | 0.0 (-1.7, 2) | -0.5 (-18.8, 21.5) |
| | Deprived | 2000-2010 | 30.3 (23.0, 37.5) | 0.6 (-0.3, 1.6) | 6.6 (-3.7, 18.1) | 2.0 (-1, 6.4) | 21.6 (-10.7, 70.1) |
| AgGr65-79 | Affluent | 2000-2001 | 137.6 (127.3, 147.8) | 0.0 (-6.1, 6.5) | 0.0 (-12.2, 13) | 0.0 (-4.0, 5.1) | 0.0 (-8.1, 10.2) |
| | | 2001-2007* | 137.9 (130.8, 145.1) | -2.5 (-3.8, -1.1) | -17.3 (-26.3, -7.4) | -1.8 (-2.6, -0.8) | -12.6 (-18.3, -5.6) |
| | | 2007-2010 | 120.5 (114.6, 126.4) | 0.6 (-2.0, 3.3) | 2.4 (-8.1, 13.2) | 0.5 (-1.6, 2.8) | 2.0 (-6.5, 11.3) |
| | Medium | 2000-2010 | 136.4 (125.9, 146.8) | -1.1 (-2.4, 0.2) | -11.8 (-26.3, 2.3) | -0.8 (-1.7, 0.2) | -8.6 (-18.2, 1.8) |
| | Deprived | 2000-2004 | 139.8 (119.8, 159.8) | -1.5 (-6.2, 3.2) | -7.4 (-31.1, 16.2) | -1.1 (-4, 2.5) | -5.3 (-19.9, 12.7) |
| | | 2004-2010* | 132.8 (120.8, 144.9) | 5.9 (1.9, 10.2) | 41.6 (13.2, 71.4) | 4.4 (1.4, 7.9) | 31.1 (9.9, 55.5) |
| AgGr80mais | Affluent | 2000-2006 | 719.7 (670.8, 768.5) | -0.8 (-9.1, 7.6) | -5.6 (-63.6, 53.2) | -0.1 (-1.2, 1.1) | -0.8 (-8.3, 7.9) |
| | | 2006-2010* | 713.1 (685.4, 740.8) | 11.1 (0.5, 20.8) | 55.3 (2.7, 103.9) | 1.6 (0.1, 3.0) | 7.8 (0.4, 14.9) |
| | Medium | 2000-2003 | 660.3 (592.3, 728.4) | 11.5 (-8.8, 31.4) | 45.8 (-35.0, 125.6) | 1.7 (-1.3, 5.2) | 7.0 (-5.1, 20.7) |
| | | 2003-2007* | 706.0 (661.0, 751.0) | -16.2 (-28.3, -4.6) | -81.0 (-141.4, -22.8) | -2.3 (-3.8, -0.7) | -11.5 (-19.1, -3.4) |
| | | 2007-2010 | 625.1 (586.0, 664.2) | 3.5 (-13.0, 20.0) | 13.8 (-52.0, 80.2) | 0.5 (-2.0, 3.3) | 2.2 (-8.0, 13.3) |
| | Deprived | 2000-2006 | 726.5 (638.8, 814.1) | -4.8 (-19.1, 9.9) | -33.3 (-133.7, 69.1) | -0.7 (-2.4, 1.6) | -4.6 (-16.5, 10.9) |
| | | 2006-2010 | 694.3 (644.9, 743.6) | 12.2 (-6.0, 31.0) | 60.8 (-29.8, 154.9) | 1.7 (-0.8, 4.6) | 8.7 (-4.2, 23.1) |

AgGr – Age Group, SES – Regional socioeconomic status, AIR – age-specific incidence rates, per 100,000 persons-year, in the beginning of the period, AAC – Annual absolute change, per 100,000 persons-year, PAC – Period absolute change, per 100,000 persons-year, ARC – Annual relative change (%),PRC – Period relative change (%), * p<0.05 for temporal trend (significant change)

## Discussion

In this study, we aimed to analyze the temporal trends of age-specific incidence rates of hip fractures, by sex, age groups, and regional socioeconomic status in Portugal, during the BJD (2000-2010). We found socioeconomic, age and sex inequalities in temporal trends. Inequalities are avoidable differences and usually linked to unequal opportunities of access to prevention or treatment[30].

For the oldest women (≥ 80 years-old) the SES inequalities in the trends seem to vanish, and this might be because social inequalities can diminish with age[31]. The most disadvantaged survivors are in general very healthy since the less healthy will have less probability to reach older age[31]. Only women aged 65-79 years-old, in the affluent regions, have a continuously decreasing trend during all the study period. The strongest inequalities were observed in women between 65-79 years-old and increased during the BJD: while HF incidence persistently decreases in the affluent regions, the decrease in the medium regions was only for a short period of three years and, in the deprived regions, there was no decreasing period; besides, there are increasing trends starting first in 2006 in the deprived regions and after, in 2007, in the medium regions. Our results seem to show that HF reduction from 2000-2010 have mainly reached a restricted group: women 65-79 years-old in the affluent regions, the preferential target population for medication and treatment against osteoporosis and HF[32, 33] while sustainable reduction seems to have failed for all the other men and women. All stable or increasing trends in 2000 (for all age groups and regional SES among women) turned to accentuate decreasing trends around 2002/2003, although such turning points were rarely observed for men. Abrupt changes in epidemiological trends are usually compatible with interventions, or other events affecting population health, rather than with the natural development of a disease. Apparently, in the beginning of BJD, there were positive efforts to reduce HF. A National Program Against Rheumatic Disease (NPARD) was implemented by the Ministry of Health as a contribution to the BJD initiative. The program put these diseases in the national political agenda, by pooling efforts of services and levels of health care provision, and investment on primary, secondary and tertiary prevention. The NPARD had the final goal of inverting the increasing trend of the problem[34]. Also, a previous study identified a sales increase, around 2003, of the first-line medication against osteoporosis, mainly bisphosphonates, coincident with decreasing trends of HF incidence among women in the 65-79 year-old age group [35]. However, our results show that in most of the analyzed groups the decreasing trends last for short periods and new turning points with increasing trends started in 2006/2007, continuing until 2010 and nullifying the positive effect of the decreasing periods – at the end of the BJD, the age-specific incidence rates in women (except those from affluent regions, with ages 65-79 years) are in the same magnitude, or even higher, than in the beginning of the BJD and the SES inequalities deepened. Some reasons might explain the abrupt turning points to increasing trends after 2006/2007. The well-being of the population worsened, especially in the elderly (≥65 years) due to a revision (lowering) of the pensions in 2007[36]. Since 2007, the economic scenario has worsened as Portugal faced severe consequences of the global economic/financial crisis[37]. Experience and evidence from past recessions show a negative impact of austerity policies on heath inequality[38]. Recession periods can impact people´s lifestyle in several ways, which in turn might affect long-term HF rates although we would expect that such an impact would reflect smooth changes in the trends of HF. Abrupt changes, such as what we observed, are more likely to be due to abrupt changes in society with impacts on the population. The abrupt turn from decrease to increase HF rates could be due to changes in the guidelines for prescriptions of anti-osteoporosis medication, for instance. An analysis of medical prescriptions in the study period could have been elucidative. Unfortunately, such data were not available. However, there is no reason to believe that during the study period physicians reduced the prescriptions since there was neither public disinvestment in health [37] nor changes in the Portuguese guidelines for osteoporotic treatment. Reduction in anti-osteoporosis medication prescriptions could also be due to new evidence about the adverse effects of long-term use of bisphosphonates[39, 40]. Nevertheless, this hypothesis does not seem to be a reasonable explanation for the observed differences in trends of HF because a reduction in prescriptions, whatever the reason, would affect all the SES-age-sex-groups equally. Loss of adherence to anti-osteoporosis treatment could explain the increasing trends after 2006/2007. In the USA, studies evaluating the adherence to osteoporosis medications pointed out the main reasons for abandonment: drug-related side effects, having multiple comorbid conditions and higher cost[41, 42]. In Portugal, some patients reported difficulties in the access of medicaments due to economic constraints, drugs for chronic conditions being among those that patients most often fail to acquire[37]. The percentage of government participation in the costs of medications in Portugal varies according to the disease to be treated/controlled. Anti-osteoporotic medicaments (including generic ones) are only partially supported by the government; therefore, all patients need to contribute a certain percentage (which varies according to the medication). For older patients (which tend to be poly-medicated) and for the most deprived patients, any cost, though small, might be a heavy burden on the budget. The more vulnerable segment of the population is usually more adversely affected by poverty, job insecurity, unemployment, and privatization of goods and services. Vulnerability results from an interaction between developmental problems, personal incapacities, disadvantaged social status, the inadequacy of interpersonal networks and supports, degraded neighborhoods and environments[43]. In times of crisis, there is expected to be a deterioration of health care seeking, various effects on providers, and a disease burden that will especially affect the most deprived and the elderly population[37]. The loss of adherence due to economic constraints is a plausible explanation for the trend patterns observed since the elderly and the more deprived population were the most affected by the economic crisis and it is in these groups that increasing trends were observed after 2007. Moreover, the absence of a lag time between economic crisis and the increasing turning points corroborates the hypothesis of loss of adherence of anti-osteoporotic medication[35]. Most of the studies on the health effects of the economic crisis have analyzed aggregate data focusing on population averages, and may have hidden the existent inequalities between SES. Our supplementary material is an example of this; we present the results of an analysis for the whole period in each age and sex group, but without SES stratification, and we lose the capacity to identify differences among groups. We observed roughly the same pattern in all sex and age groups (two turning points), except for men aged 50-64 year-old, and at different scales (supplementary methods 2, supplementary figure 1 and 2 and supplementary table 3 and 4). It seems that analyzing aggregated data (as most of the published studies do) may hide SES inequalities. For example, in our study, when we analyzed HF without stratifying by SES groups, we do not identify the decreasing trend of HF in women aged 65-79 years-old in affluent areas. In addition, inequalities tend to rise during recessions since affluent SES are better at adapting to new and changing economic circumstances than the deprived SES. Among men there are also SES inequalities in the trends, although not so evident as among women[44].

We found age inequalities in the temporal trends of HF incidence, with the oldest women in a disadvantageous position. Only women over 80 years-old, show increasing trends in all the SES regions after 2006/2007, reinforcing our hypothesis that the economic crisis in Portugal, which had a high impact on the elderly regardless of their SES, may have contributed to the observed trends. The elderly are usually poly-medicated due to several comorbidities and the anti-osteoporosis medication is among the first abandoned medications[41, 45] in the face of economic constraints. Furthermore, only for women ≥ 80 years from deprived regions was there an increasing trend in the beginning of the BJD and the later observed decreasing periods were shorter in this age group. This might reflect age inequalities in the priorities of intervention actions, targeting younger women while the oldest are neglected[43]. In general, temporal trends are more stable in the youngest group of 50-64 year-olds. Statistically, there is only one significant reduction period among women with ages 50-64 years-old (0.6 HF per 100,000 per person-year in affluent SES). However, the magnitude of this reduction is too small and might arguibly be clinically irrelevant.

There are sex inequalities evident in the trends: during the study period women in all age groups and SES regions (except <80 years-old in deprived regions) presented periods of significant decreasing trends in the age-specific incidence rates. Among men, a reduction was observed only in two groups: 65-79 years-old in affluent regions, and ≥80 years-old in the medium regions. In general, trends among men are stable and this might be a consequence of the lack of attention to men´s bone health. Frequently, osteoporosis and HF are seen as a woman´s problem and less attention is given to men in both prevention programs and drug therapy. In men drug therapy has never reached the level that it has in women[46]; although, with their increasing longevity, more men will be at risk for osteoporosis and HF[44] and interventions must be more inclusive to men.

A limitation of our study is the nonexistence of individual data for the patients' SES characterization because the individual's socioeconomic data is not routinely collected. Therefore, any conclusions need to be treated with caution, even though the socioeconomic status of the place of residence is frequently and adequately used as a proxy for individual socioeconomic status[10, 47]. Furthermore, the measures of municipality SES are helpful to recognize geographical areas at high-risk of HF in order to better direct public health intervention programs. Recurrent fractures could not be identified because of confidentiality issues (the patient unique identifier was not available), and this could be seen as a limitation since the risk of a new fragility fracture increases after the primary HF. However, our study focused on incidence rates of HF (number of HF in a population at risk) rather than cumulative incidence (number of persons with an HF in a population at risk) and, therefore, such a limitation does not bias our results.

Our study has the advantage of using population based on repeated cross-sectional data from a nationwide register and stratifies the HF incidence per SES regions, sex and age groups, allowing the identification of different effects on trends and clarifying hidden inequalities in the trends. The use of a multidimensional SES that encapsulates a variety of domains, related to building, households, families, and individual characteristics, and determined by an approach that allows reduction of the covariates to a set of uncorrelated variables that explain much of the original data can be seen as an advantage. Despite the focus that the BJD brought to studies on HF, little attention has been given to the inequalities associated with this disorder and, to our knowledge, this is the first study analyzing the temporal trends of HF incidence by sex and age group for different SES regions.

Our results can give insights about the real burden of HF and help with the better planning of health policies. Understanding positive and negative aspects of the initiatives triggered by BJD may help to potentiate better results in the ongoing global alliance for musculoskeletal health. In general, the abrupt decreasing turning points found in our study seem to be plausibly explained by an intervention, likely based on increased treatment (e.g. anti-osteoporosis medication) and prevention programs observed since the beginning of the BJD, with an impact on the incidence rates in all ages and SES groups among women. Coincident with the beginning of the economic crisis in Portugal, the most deprived and oldest groups returned to increased trends, reaching similar or even higher rates in 2010 than those observed in 2000.

## Conclusions

There are socioeconomic, age and sex inequalities in temporal trends of age-specific incidence rates in Portugal during the BJD. The inequalities in trends are especially marked in women between 65-79 years-old: only those living in affluent areas have a continuously decreasing trend while the medium and deprived regions have increasing trends after 2007. The SES inequalities observed in women < 80 years-old disappear in the oldest age group (≥ 80 years-old). It seems that HF prevention during the BJD in Portugal has reached mainly women (65-79 years-old) in the affluent areas while it has failed for all the other age groups. Clear sex inequalities were observed: only two groups of SES/age in men presented a decreasing period, as opposed to the majority of SES/age groups in women. Overall, the trends among men are stable, which could reflect the lack of attention given to bone health among men.

Despite some successful periods of decreasing trends, at the end of the Bone and Joint Decade, the incidence rates returned to the values of 2000, or even higher, in almost all age groups, both in men and women.

**Acknowledgments**: This work had the financial support of Fundação para a Ciência e a Tecnologia FCT / MEC through National Funds within the framework of the project PTDC/SAU-EPI/113424/2009 and co-financed by the FEDER via the PT2020 Partnership Agreement under the 4293 Unit I&D.

We acknowledge the Central Administration of Health Services (ACSS) for the data from the National Hospital Discharge Register.

**Conflict of Interest**: Carla Maria Oliveira, Sandra Maria Alves, and Maria Fátima Pina declare that they have no conflict of interest.

**Role of funding source**: The funder Fundação para a Ciência e Tecnologia - FCT has no role in this paper.

**Authors' contributions:** CMO and MFP designed the study. CMO developed the statistical analysis, interpreted the results and draft the manuscript. SMA contributed to the interpretation of results and helped to draft the manuscript. MFP supervised the research, helped to draft the manuscript and reviewed the manuscript. All authors read and approved the final manuscript.

## References

1. Wilkins CH, Birge SJ. Prevention of osteoporotic fractures in the elderly. The American journal of medicine. 2005;118(11):1190-5. Epub 2005/11/08.

2. Hernlund E, Svedbom A, Ivergard M, Compston J, Cooper C, Stenmark J, et al. Osteoporosis in the European Union: medical management, epidemiology and economic burden. A report prepared in collaboration with the International Osteoporosis Foundation (IOF) and the European Federation of Pharmaceutical Industry Associations (EFPIA). Archives of osteoporosis. 2013;8:136. Epub 2013/10/12.

3. BJD. The bone and joint decade. Global alliance for musculoskeletal heath. 2015 [cited 20015 06-11-2015]; Available from: http://bjdonline.org/.

4. Woolf AD. The bone and joint decade 2000-2010. Annals of the rheumatic diseases. 2000;59(2):81-2. Epub 2000/02/09.

5. Mackenbach JP. Health Inequalities: Europe in Profile. WHO European Region. UK, 2006.

6. Woolf AD. Bone and Joint Decade report: moving together beyond the decade. Preface. Best practice & research Clinical rheumatology. 2012;26(2):167-8. Epub 2012/07/17.

7. Adler NE, Newman K. Socioeconomic disparities in health: pathways and policies. Health Aff (Millwood). 2002;21(2):60-76. Epub 2002/03/20.

8. Wilkinson R, Marmot M. Social determinants of health: the solid facts. Copenhagen, Denmark: World Health Organization Europe, 2003.

9. Brennan SL, Pasco JA, Urquhart DM, Oldenburg B, Wang Y, Wluka AE. Association between socioeconomic status and bone mineral density in adults: a systematic review. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA. 2011;22(2):517-27. Epub 2010/05/08.

10. Brennan SL, Pasco JA, Urquhart DM, Oldenburg B, Hanna F, Wluka AE. The association between socioeconomic status and osteoporotic fracture in population-based adults: a systematic review. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA. 2009;20(9):1487-97. Epub 2008/12/25.

11. Adler NE, Newman K. Socioeconomic disparities in health: pathways and policies. Health Aff (Millwood). 2002;21(2):60-76. Epub 2002/03/20.

12. Pampel FC, Krueger PM, Denney JT. Socioeconomic Disparities in Health Behaviors. Annual review of sociology. 2010;36:349-70. Epub 2011/09/13.

13. Cheng SY, Levy AR, Lefaivre KA, Guy P, Kuramoto L, Sobolev B. Geographic trends in incidence of hip fractures: a comprehensive literature review. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA. 2011;22(10):2575-86. Epub 2011/04/13.

14. de Pina MF, Alves SM, Barbosa M, Barros H. Hip fractures cluster in space: an epidemiological analysis in Portugal. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA. 2008;19(12):1797-804. Epub 2008/06/10.

15. Hagino H, Katagiri H, Okano T, Yamamoto K, Teshima R. Increasing incidence of hip fracture in Tottori Prefecture, Japan: trend from 1986 to 2001. Osteoporos Int. 2005;16(12):1963-8. Epub 2005/09/01.

16. Kannus P, Niemi S, Parkkari J, Palvanen M, Vuori I, Jarvinen M. Hip fractures in Finland between 1970 and 1997 and predictions for the future. Lancet. 1999;353(9155):802-5. Epub 1999/08/25.

17. Ballane G, Cauley JA, Luckey MM, Fuleihan Gel H. Secular trends in hip fractures worldwide: opposing trends East versus West. Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research. 2014;29(8):1745-55. Epub 2014/03/20.

18. Kannus P, Niemi S, Parkkari J, Palvanen M, Vuori I, Jarvinen M. Nationwide decline in incidence of hip fracture. Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research. 2006;21(12):1836-8. Epub 2006/09/28.

19. Dimai HP, Svedbom A, Fahrleitner-Pammer A, Pieber T, Resch H, Zwettler E, et al. Epidemiology of hip fractures in Austria: evidence for a change in the secular trend. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA. 2011;22(2):685-92. Epub 2010/05/12.

20. Briot K, Maravic M, Roux C. Changes in number and incidence of hip fractures over 12years in France. Bone. 2015;81:131-7. Epub 2015/07/15.

21. Piscitelli P, Feola M, Rao C, Celi M, Gasbarra E, Neglia C, et al. Ten years of hip fractures in Italy: For the first time a decreasing trend in elderly women. World journal of orthopedics. 2014;5(3):386-91. Epub 2014/07/19.

22. Melton LJ, 3rd, Kanis JA, Johnell O. Potential impact of osteoporosis treatment on hip fracture trends. J Bone Miner Res. 2005;20(6):895-7. Epub 2005/05/11.

23. Feder G, Cryer C, Donovan S, Carter Y. Guidelines for the prevention of falls in people over 65. The Guidelines' Development Group. BMJ. 2000;321(7267):1007-11. Epub 2000/10/20.

24. Population Ageing in the United Kingdom, its Constituent Countries and the European Union. http://www.ons.gov.uk/ons/dcp171776_258607.pdf2012 [cited 2014 14-12-2104].

25. INE. *Instituto Nacional de Estatística*; [cited 2012]; Available from: www.ine.pt.

26. ACSS. Auditoria da codificação clínica [Clinical codification Audits]. 2011 Available from: http://portalcodgdh.min-saude.pt/index.php/Auditoria_da_codificação_cl%C3%ADnica.

27. Barros PP, Machado SR, Simoes Jde A. Portugal. Health system review. Health systems in transition. 2011;13(4):1-156. Epub 2012/01/10.

28. Alves SM, Castiglione D, Oliveira CM, de Sousa B, Pina MF. Age-period-cohort effects in the incidence of hip fractures: political and economic events are coincident with changes in risk. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA. 2014;25(2):711-20. Epub 2013/08/29.

29. Oliveira CM, Economou T, Bailey T, Mendonca D, Pina MF. The interactions between municipal socioeconomic status and age on hip fracture risk. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA. 2015;26(2):489-98. Epub 2014/10/26.

30. Braveman PA, Kumanyika S, Fielding J, Laveist T, Borrell LN, Manderscheid R, et al. Health disparities and health equity: the issue is justice. American journal of public health. 2011;101 Suppl 1:S149-55. Epub 2011/05/10.

31. Jefferys M. Social inequalities in health--do they diminish with age? American journal of public health. 1996;86(4):474-5. Epub 1996/04/01.

32. NCGC. Osteoporosis: Fragility Fracture Risk. Osteoporosis: Assessing the Risk of Fragility Fracture. London: NCGC, National Clincal Guideline Centre, 2012.

33. Etxebarria-Foronda I, Arrospide A, Soto-Gordoa M, Caeiro JR, Abecia LC, Mar J. Regional variability in changes in the incidence of hip fracture in the Spanish population (2000-2012). Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA. 2015;26(5):1491-7. Epub 2015/01/13.

34. Lucas R, Monjardino M. O estado da Reumatologia em Portugal. 2010.

35. Alves SM, Economou T, Oliveira C, Ribeiro AI, Neves N, Gomez-Barrena E, et al. Osteoporotic hip fractures: Bisphosphonates sales and observed turning point in trend. A population-based retrospective study. Bone. 2012. Epub 2013/01/01.

36. Murteira MC. A reforma de 2007 do sistema público de pensões em Portugal - uma análise crítica das escolhas normativas implícitas. Faculdade de Economia da Universidade de Coimbra, 2008.

37. Sakellarides C, Castelo-Branco L, Barbosa P, Azevedo H. The impact of the financial crisis on the health system and health in Portugal. Copenhagen, Denmark: World Health Organization, 2014.

38. Bacigalupe A, Escolar-Pujolar A. The impact of economic crises on social inequalities in health: what do we know so far? International journal for equity in health. 2014;13:52. Epub 2014/07/27.

39. Kennel KA, Drake MT. Adverse effects of bisphosphonates: implications for osteoporosis management. Mayo Clinic proceedings. 2009;84(7):632-7; quiz 8. Epub 2009/07/02.

40. Salari P, Abdollahi M. Long term bisphosphonate use in osteoporotic patients; a step forward, two steps back. Journal of pharmacy & pharmaceutical sciences : a publication of the Canadian Society for Pharmaceutical Sciences, Societe canadienne des sciences pharmaceutiques. 2012;15(2):305-17. Epub 2012/05/15.

41. Yun H, Curtis JR, Guo L, Kilgore M, Muntner P, Saag K, et al. Patterns and predictors of osteoporosis medication discontinuation and switching among Medicare beneficiaries. BMC musculoskeletal disorders. 2014;15:112. Epub 2014/04/02.

42. Tosteson AN, Do TP, Wade SW, Anthony MS, Downs RW. Persistence and switching patterns among women with varied osteoporosis medication histories: 12-month results from POSSIBLE US. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA. 2010;21(10):1769-80. Epub 2010/01/27.

43. Mechanic D, Tanner J. Vulnerable people, groups, and populations: societal view. Health Aff (Millwood). 2007;26(5):1220-30. Epub 2007/09/13.

44. Adler RA. Osteoporosis in men: a review. Bone Res. 2014;2:14001. Epub 2014/01/01.

45. Modi A, Sajjan S, Gandhi S. Challenges in implementing and maintaining osteoporosis therapy. International journal of women's health. 2014;6:759-69. Epub 2014/08/26.

46. Willson T, Nelson SD, Newbold J, Nelson RE, LaFleur J. The clinical epidemiology of male osteoporosis: a review of the recent literature. Clinical epidemiology. 2015;7:65-76. Epub 2015/02/07.

47. Guillemin F, Carruthers E, Li LC. Determinants of MSK health and disability--social determinants of inequities in MSK health. Best practice & research Clinical rheumatology. 2014;28(3):411-33. Epub 2014/12/08.

.

**Supplementary table 1 – Number of hip fracture and population (2000 – 2010) by socioeconomic status regions, age groups and sex**

| | | Women | | | | | | Men | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Affuent | | Medium | | Deprived | | Affuent | | Medium | | Deprived | |
| AgGr | Year | Nfrat | Npop | Nfrat | Npop | Nfrat | Npop | Nfrat | Npop | Nfrat | Npop | Nfrat | Npop |
| 50_64 | 2000 | 193 | 582540 | 57 | 225965 | 34 | 78129 | 135 | 528088 | 46 | 201070 | 18 | 68007 |
| | 2001 | 199 | 592173 | 86 | 228116 | 27 | 76091 | 138 | 537320 | 61 | 204152 | 20 | 66841 |
| | 2002 | 166 | 603158 | 79 | 230934 | 37 | 74991 | 125 | 546860 | 37 | 208324 | 25 | 66505 |
| | 2003 | 216 | 612555 | 90 | 232659 | 32 | 73619 | 136 | 555006 | 67 | 211055 | 22 | 66023 |
| | 2004 | 181 | 622241 | 67 | 235562 | 20 | 72697 | 129 | 563314 | 66 | 215218 | 23 | 66010 |
| | 2005 | 184 | 633645 | 83 | 239748 | 22 | 72242 | 133 | 573495 | 59 | 219943 | 22 | 66263 |
| | 2006 | 184 | 643563 | 77 | 243089 | 26 | 71896 | 133 | 581537 | 53 | 224198 | 21 | 66702 |
| | 2007 | 167 | 653480 | 69 | 246857 | 23 | 71697 | 152 | 589713 | 54 | 228797 | 21 | 67296 |
| | 2008 | 192 | 660911 | 69 | 250264 | 35 | 71500 | 149 | 596040 | 70 | 232771 | 23 | 67967 |
| | 2009 | 196 | 667147 | 76 | 253442 | 15 | 71318 | 150 | 602046 | 56 | 237351 | 28 | 68517 |
| | 2010 | 225 | 673167 | 72 | 256810 | 38 | 71167 | 153 | 608377 | 61 | 241855 | 25 | 69310 |
| 65_79 | 2000 | 1468 | 433881 | 562 | 196942 | 276 | 88863 | 432 | 329271 | 210 | 157521 | 101 | 71745 |
| | 2001 | 1538 | 441165 | 646 | 200074 | 308 | 88968 | 496 | 335079 | 225 | 159847 | 100 | 71406 |
| | 2002 | 1403 | 448122 | 626 | 202779 | 273 | 88760 | 439 | 340982 | 209 | 161597 | 104 | 70792 |
| | 2003 | 1546 | 453842 | 631 | 205179 | 292 | 88320 | 500 | 346788 | 250 | 163643 | 85 | 69934 |
| | 2004 | 1418 | 459253 | 654 | 207284 | 285 | 87574 | 452 | 352560 | 213 | 164960 | 90 | 68908 |
| | 2005 | 1354 | 462885 | 617 | 207709 | 252 | 85920 | 440 | 357342 | 178 | 165457 | 92 | 67197 |
| | 2006 | 1410 | 464848 | 566 | 207529 | 257 | 84034 | 464 | 360706 | 221 | 164844 | 84 | 65147 |
| | 2007 | 1336 | 469219 | 491 | 208426 | 239 | 82565 | 400 | 366411 | 195 | 164984 | 84 | 63469 |
| | 2008 | 1400 | 474814 | 592 | 208844 | 244 | 80911 | 460 | 372678 | 215 | 165462 | 93 | 61586 |
| | 2009 | 1385 | 482281 | 591 | 209918 | 294 | 79416 | 467 | 379752 | 214 | 165760 | 112 | 60149 |
| | 2010 | 1381 | 489641 | 604 | 211053 | 269 | 77689 | 478 | 386874 | 215 | 166157 | 100 | 58369 |
| 65_79 | 2000 | 2107 | 126431 | 899 | 61538 | 433 | 30585 | 464 | 63583 | 225 | 36007 | 135 | 18734 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 2001 | 2190 | 130499 | 981 | 63929 | 541 | 31549 | 467 | 66794 | 275 | 37785 | 141 | 19228 |
| 2002 | 2282 | 134254 | 1056 | 65954 | 537 | 32380 | 496 | 69257 | 264 | 39121 | 140 | 19633 |
| 2003 | 2401 | 138144 | 1069 | 67858 | 573 | 33077 | 520 | 71801 | 298 | 40257 | 140 | 20157 |
| 2004 | 2503 | 144054 | 1138 | 70633 | 591 | 34320 | 574 | 75658 | 300 | 42160 | 153 | 20857 |
| 2005 | 2613 | 149394 | 1003 | 73211 | 572 | 35280 | 551 | 78228 | 280 | 43627 | 158 | 21470 |
| 2006 | 2535 | 156303 | 1027 | 76551 | 567 | 36697 | 569 | 81720 | 305 | 45584 | 152 | 22182 |
| 2007 | 2562 | 161646 | 988 | 79089 | 525 | 37481 | 590 | 84417 | 258 | 47074 | 141 | 22563 |
| 2008 | 2746 | 167697 | 1265 | 82104 | 655 | 38211 | 643 | 87721 | 323 | 48626 | 150 | 22997 |
| 2009 | 2944 | 173047 | 1208 | 84593 | 664 | 39094 | 663 | 90880 | 315 | 50217 | 184 | 23220 |
| 2010 | 3222 | 180060 | 1382 | 87818 | 704 | 39881 | 755 | 95180 | 335 | 52058 | 184 | 23625 |

AgGr - Age Group; Nfrat – number of fractures; Npop – number of population

**Supplementary methods 1 – Period absolute change, annual absolute change, period relative change and annual relative change calculation**

The period absolute change $(PAC)$ in age-specific or age-standardized incidence hip fracture rates $(IR)$ between two time points $[t_1, t_2[$ is calculated by subtracting the $IR$ of the first study year from that of the last study year. The result is expressed per 100,000 persons-year.

$$PAC_{[t_1,t_2[} = IR_{t2} - IR_{t1}$$

The annual absolute change $(AAC)$ in $IR$ between two time points $[t_1, t_2[$ is calculated by divide the period absolute change by the number of years between the two time points. The result is expressed per 100,000 persons-year.

$$AAC_{[t_1,t_2[} = \frac{IR_{t2} - IR_{t1}}{t2 - t1 + 1}$$

The period relative change $(PRC)$ in $IR$ between two time points $[t_1, t_2[$ is calculated by dividing the period absolute change by the first rate. The result is expressed in % change in the period.

$$PRC_{[t_1,t_2[} = \frac{IR_{t2} - IR_{t1}}{IR_{t1}}$$

The annual relative change $(ARC)$ in $IR$ between two time points $[t_1, t_2[$ is calculated by dividing the period relative change by the number of years between the two time points. The result is expressed in % change/year.

$$ARC_{[t_1,t_2[} = \frac{PRC_{[t_1,t_2[}}{t2 - t1 + 1}$$

**Supplementary table 2 – Estimated age-specific incidence rates of hip fracture, per 100,000 persons-year, (95% confidence interval) by socioeconomic status regions and age groups in both sexes by year (2000 – 2010)**

| AgGr | Year | Women | | | Men | | |
|---|---|---|---|---|---|---|---|
| | | Affluent | Medium | Deprived | Affluent | Medium | Deprived |
| 50-64 | 2000 | 33.2 (29.5, 36.9) | 30.1 (24.4, 35.7) | 42.6 (32.1, 53.0) | 24.4 (21.9, 26.9) | 26.0 (22.1, 30.0) | 30.3 (23.0, 37.5) |
| | 2001 | 32.3 (29.8, 34.8) | 32.7 (28.5, 36.9) | 40.9 (33.4, 48.4) | 24.3 (22.3, 26.4) | 26.0 (22.7, 29.4) | 30.9 (24.5, 37.3) |
| | 2002 | 31.5 (29.2, 33.7) | 34.3 (30.4, 38.3) | 39.3 (33.0, 45.7) | 24.3 (22.5, 26.0) | 26.0 (23.1, 28.9) | 31.5 (25.9, 37.1) |
| | 2003 | 30.7 (28.5, 32.9) | 34.5 (30.6, 38.5) | 37.7 (31.8, 43.7) | 24.2 (22.7, 25.8) | 26.0 (23.5, 28.5) | 32.1 (27.3, 37.0) |
| | 2004 | 29.8 (27.7, 31.9) | 33.7 (29.8, 37.6) | 36.3 (30.5, 42.1) | 24.2 (22.8, 25.6) | 26.0 (23.8, 28.2) | 32.8 (28.4, 37.2) |
| | 2005 | 28.9 (26.8, 31.0) | 32.5 (28.7, 36.2) | 35.5 (29.8, 41.3) | 24.3 (22.9, 25.6) | 26.0 (24.0, 28.0) | 33.5 (29.3, 37.6) |
| | 2006 | 28.3 (26.3, 30.3) | 31.1 (27.5, 34.7) | 35.5 (29.7, 41.2) | 24.3 (22.9, 25.7) | 26.0 (23.9, 28.1) | 34.1 (29.8, 38.5) |
| | 2007 | 28.2 (26.2, 30.2) | 29.8 (26.3, 33.3) | 36.1 (30.3, 42.0) | 24.4 (22.9, 25.9) | 26.0 (23.6, 28.3) | 34.8 (29.9, 39.8) |
| | 2008 | 28.8 (26.8, 30.9) | 28.9 (25.5, 32.4) | 37.3 (31.1, 43.5) | 24.5 (22.9, 26.2) | 25.9 (23.2, 28.7) | 35.5 (29.7, 41.4) |
| | 2009 | 30.1 (27.8, 32.4) | 28.5 (24.8, 32.1) | 39.0 (31.4, 46.5) | 24.7 (22.7, 26.6) | 25.9 (22.8, 29.1) | 36.2 (29.2, 43.2) |
| | 2010 | 31.8 (28.4, 35.2) | 28.1 (22.9, 33.3) | 41.2 (30.6, 51.8) | 24.8 (22.4, 27.2) | 25.9 (22.2, 29.6) | 37.0 (28.7, 45.3) |
| 65-79 | 2000 | 342.6 (331.5, 353.7) | 289.0 (266.2, 311.8) | 323.3 (293.1, 353.6) | 137.6 (127.3, 147.8) | 136.4 (125.9, 146.8) | 139.8 (119.8, 159.8) |
| | 2001 | 335.0 (326.4, 343.7) | 315.3 (295.1, 335.5) | 324.4 (303.2, 345.6) | 137.9 (130.8, 145.1) | 135.1 (126.3, 143.9) | 137.3 (122.9, 151.7) |
| | 2002 | 327.6 (320.5, 334.7) | 312.0 (292.7, 331.3) | 322.6 (302.9, 342.3) | 136.8 (130.2, 143.3) | 133.8 (126.4, 141.3) | 134.9 (122.6, 147.3) |
| | 2003 | 320.4 (314.0, 326.7) | 311.6 (292.7, 330.5) | 318.9 (299.3, 338.4) | 134.4 (127.9, 140.8) | 132.6 (126.2, 139.0) | 133.2 (121.2, 145.1) |
| | 2004 | 313.3 (307.3, 319.4) | 310.8 (292.1, 329.5) | 312.8 (293.5, 332.1) | 130.4 (124.2, 136.7) | 131.3 (125.6, 137.0) | 132.8 (120.8, 144.9) |
| | 2005 | 306.7 (300.8, 312.6) | 297.7 (279.5, 315.8) | 306.4 (287.4, 325.4) | 126.2 (120.2, 132.3) | 130.1 (124.7, 135.6) | 134.3 (122.1, 146.6) |
| | 2006 | 300.5 (294.7, 306.4) | 266.8 (249.8, 283.7) | 303.8 (284.7, 322.9) | 122.8 (116.8, 128.7) | 129.0 (123.3, 134.6) | 138.0 (125.5, 150.6) |
| | 2007 | 294.8 (288.8, 300.8) | 251.7 (235.2, 268.1) | 307.3 (287.8, 326.8) | 120.5 (114.6, 126.4) | 127.9 (121.6, 134.1) | 144.3 (131.3, 157.3) |
| | 2008 | 289.5 (283.0, 295.9) | 271.3 (253.7, 288.9) | 318.7 (298.6, 338.8) | 120.4 (114.5, 126.3) | 126.8 (119.6, 134.0) | 153.1 (139.0, 167.1) |
| | 2009 | 284.4 (276.8, 291.9) | 284.0 (265.3, 302.6) | 335.7 (313.1, 358.3) | 121.5 (115.2, 127.7) | 125.8 (117.4, 134.1) | 163.6 (146.5, 180.8) |
| | 2010 | 279.4 (270.0, 288.7) | 286.5 (264.5, 308.5) | 353.3 (319.5, 387.1) | 122.8 (113.8, 131.8) | 124.8 (115.1, 134.4) | 174.9 (150.0, 199.8) |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 80+ | 2000 | 1663.2 (1599.7, 1726.8) | 1514.8 (1385.9, 1643.8) | 1486.2 (1337.4, 1635.0) | 719.7 (670.8, 768.5) | 660.3 (592.3, 728.4) | 726.5 (638.8, 814.1) |
| | 2001 | 1683.9 (1637.9, 1729.8) | 1584.4 (1490.3, 1678.5) | 1629.1 (1517.2, 1740.1) | 718.8 (684.0, 753.6) | 686.8 (638.5, 735.0) | 720.5 (656.8, 784.1) |
| | 2002 | 1709.6 (1663.8, 1755.3) | 1634.6 (1539.9, 1729.3) | 1726.3 (1612.3, 1840.2) | 718.7 (688.7, 748.6) | 702.5 (657.1, 748.0) | 714.3 (660.5, 768.1) |
| | 2003 | 1732.7 (1687.8, 1777.5) | 1632.2 (1539.2, 1725.2) | 1759.8 (1646.0, 1873.7) | 718.5 (689.5, 747.5) | 706.0 (661.0, 751.0) | 708.2 (656.9, 759.5) |
| | 2004 | 1737.0 (1693.1, 1780.9) | 1570.5 (1481.5, 1659.4) | 1736.8 (1625.7, 1847.9) | 716.8 (688.2, 745.4) | 691.2 (647.9, 734.5) | 702.6 (651.8, 753.3) |
| | 2005 | 1704.5 (1661.8, 1747.2) | 1475.8 (1392.0, 1559.6) | 1667.8 (1561.1, 1774.4) | 713.9 (685.8, 742.0) | 665.9 (624.6, 707.2) | 697.3 (647.2, 747.4) |
| | 2006 | 1644.7 (1603.7, 1685.7) | 1403.8 (1324.1, 1483.4) | 1600.2 (1497.9, 1702.4) | 713.1 (685.4, 740.8) | 640.8 (600.9, 680.6) | 694.3 (644.9, 743.6) |
| | 2007 | 1611.4 (1571.3, 1651.6) | 1401.6 (1322.1, 1481.2) | 1591.8 (1490.0, 1693.7) | 718.1 (690.8, 745.4) | 625.1 (586.0, 664.2) | 697.7 (648.9, 746.4) |
| | 2008 | 1635.3 (1594.4, 1676.1) | 1454.9 (1371.9, 1537.8) | 1648.2 (1542.4, 1754.0) | 729.7 (702.3, 757.0) | 624.9 (586.1, 663.7) | 710.9 (660.9, 761.0) |
| | 2009 | 1698.4 (1657.0, 1739.9) | 1525.8 (1438.9, 1612.7) | 1728.2 (1617.4, 1839.0) | 747.2 (716.7, 777.7) | 631.1 (590.9, 671.2) | 732.7 (674.2, 791.3) |
| | 2010 | 1783.0 (1726.4, 1839.5) | 1607.6 (1480.1, 1735.2) | 1802.0 (1640.7, 1963.3) | 768.9 (725.2, 812.6) | 639.1 (581.3, 696.8) | 758.1 (675.4, 840.8) |

AgGr – Age group

## Supplementary methods 2 – Annual time series of age-standardized of hip fracture by sex (2000 – 2010)

### Statistical analysis

We computed annual time series of the age-standardized incidence rates of HF (ASIR) expressed as discharges per 100,000 person-years (PY) stratified by sex. The ASIR was standardized using the direct method, using the 2006 European population [1] and 5-years age groups, starting with 50-54 and ending with 85+), per year.

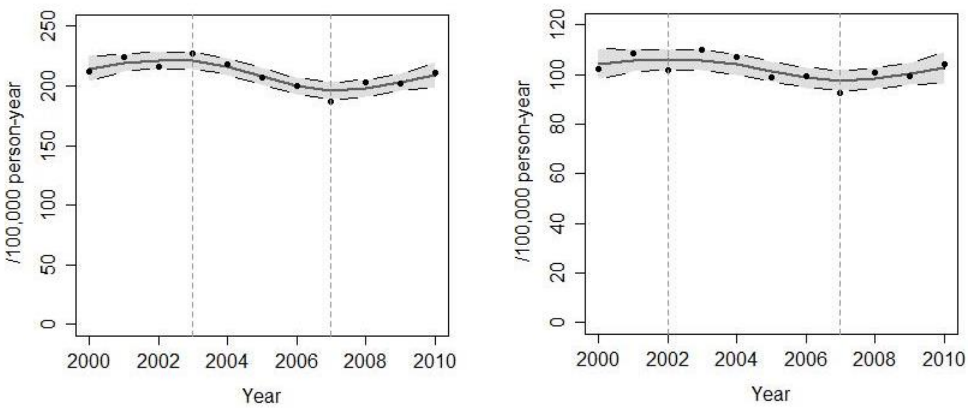
We assumed that the ASIR ($ASIR_t$) in a specific year ($t = 2000, \ldots, 2010$) follows a Gaussian distribution with mean $\mu_t$ and standard deviation $\sigma$. For each sex, the parameters of interest of ASIR were estimated by the following model:

$$ASIR_t \sim N(\mu_t, \sigma)$$

$$log(\mu_t) = \beta_0 + s\left(Year^{(t)}\right)$$

## Supplementary figure 1 – Estimated temporal trends (2000-2010) of age-standardized incidence rates of hip fracture, per 100,000 persons-year (95% confidence interval) by sex

**Women** **Men**



**Supplementary table 3 – Estimated absolute and relative changes in temporal trends (2000-2010) of age-standardized incidence rates of hip fracture, per 100,000 persons-year (95% confidence interval) by sex**

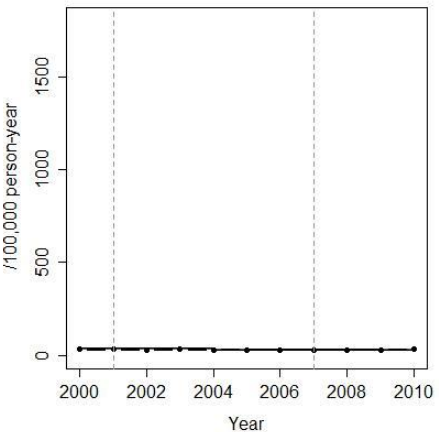
| Sex | Year | AIR | AAC | PAC | ARC | PRC |
|---|---|---|---|---|---|---|
| Women | 2000-2003 | 214.6 (204.3, 224.9) | 1.8 (-1.4, 5) | 7.2 (-5.8, 20.2) | 0.8 (-0.6, 2.4) | 3.4 (-2.6, 9.7) |
| | 2003-2007* | 221.5 (214.4, 228.6) | -5.2 (-7.1, -3.1) | -26 (-35.5, -15.5) | -2.3 (-3.1, -1.4) | -11.7 (-15.7, -7.1) |
| | 2007-2010* | 195.6 (188.5,202.7) | 3.5 (0.6, 6.6) | 13.9 (2.3, 26.6) | 1.8 (0.3, 3.4) | 7.1 (1.2, 13.8) |
| Men | 2000-2002 | 104.4 (98.2, 110.5) | 0.5 (-1.9, 2.9) | 1.5 (-5.8, 8.7) | 0.5 (-1.7, 2.9) | 1.5 (-5.2, 8.7) |
| | 2002-2007* | 106.1 (102.0, 110.2) | -1.4 (-2.3, -0.5) | -8.4 (-13.9, -3.0) | -1.3 (-2.1, -0.5) | -7.9 (-12.8, -2.9) |
| | 2007-2010 | 97.7 (93.6, 101.8) | 1.3 (-0.5, 3.2) | 5.1 (-2.0, 13.0) | 1.3 (-0.5, 3.4) | 5.2 (-2, 13.6) |

AgGr – Age Group, ASIR – age-standardized incidence rates, per 100,000 persons-year, in the beginning of the period, AAC – Annual absolute change, per 100,000 persons-year, PAC – Period absolute change, per 100,000 persons-year, ARC – Annual relative change (%), PRC – Period relative change (%), * p<0.05 for temporal trend (significant change)

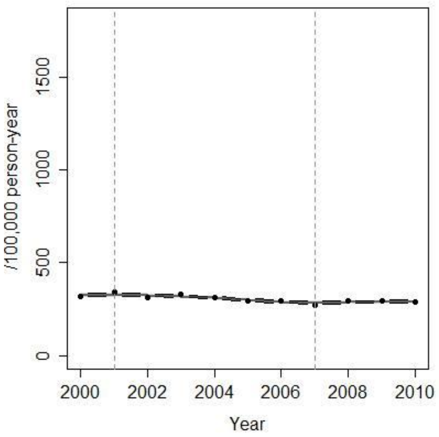
**Supplementary figure 2 – Estimated temporal trends (2000-2010) of age-specific incidence rates of hip fracture, per 100,000 persons-year (95% confidence interval) by age groups and sex**

Women

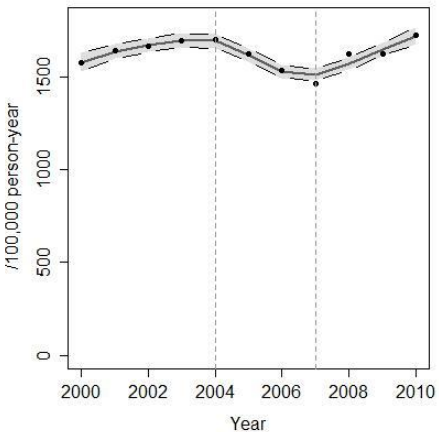
50-64




65-79

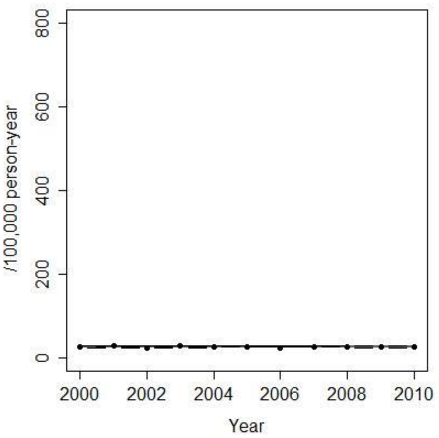



80+

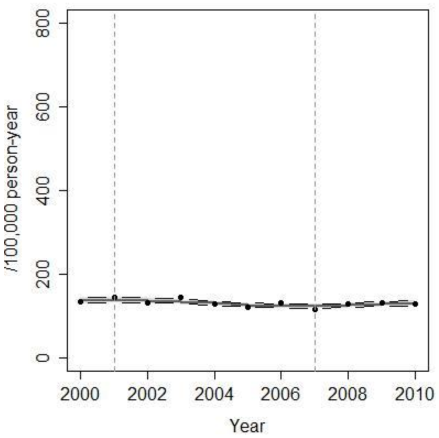



Men

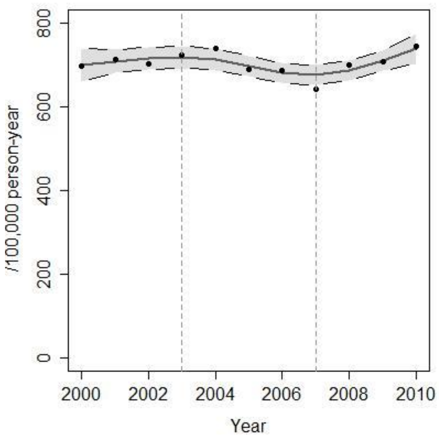
50-64




65-79




80+



**Supplementary table 4 – Estimated absolute and relative changes in temporal trends (2000-2010) of age-specific incidence rates of hip fracture, per 100,000 persons-year, (95% confidence interval) by age groups and sex**

| Sex | AgGr | Year | Age-specific incidence rates (AIR) | Annual absolute change (AAC) | Period absolute change (PAC) | Annual relative change (ARC) | Period relative change (PRC) |
|---|---|---|---|---|---|---|---|
| Women | 50_64 | 2000-2001 | 33.1 (29.9, 36.2) | 0.1 (-1.8, 1.9) | 0.1 (-3.7, 3.8) | 0.2 (-5.1, 6.2) | 0.4 (-10.2, 12.4) |
| | | 2001-2007* | 33.3 (31.1, 35.5) | -0.6 (-1.1, -0.2) | -4.5 (-7.4, -1.7) | -1.9 (-3, -0.8) | -13.6 (-21, -5.3) |
| | | 2007-2010 | 28.8 (26.9, 30.6) | 0.8 (0, 1.7) | 3.4 (-0.1, 6.9) | 2.9 (-0.1, 6.3) | 11.8 (-0.3, 25.1) |
| | 65_79 | 2000-2001 | 326.5 (314.9, 338.2) | 0.2 (-6.1, 7.4) | 0.5 (-12.1, 14.8) | 0.1 (-1.8, 2.3) | 0.1 (-3.6, 4.7) |
| | | 2001-2007* | 327.7 (319.5, 336.0) | -6.1 (-7.6, -4.6) | -42.4 (-53.2, -32.2) | -1.9 (-2.3, -1.4) | -13 (-16, -10.1) |
| | | 2007-2010 | 285.0 (277.8, 292.3) | 1.7 (-1.4, 4.8) | 6.8 (-5.5, 19.1) | 0.6 (-0.5, 1.7) | 2.4 (-1.9, 6.8) |
| | 80+ | 2000-2003* | 1577.0 (1527.2, 1626.9) | 22.9 (10.7, 34.6) | 114.3 (53.6, 172.8) | 1.5 (0.7, 2.2) | 7.3 (3.3, 11.2) |
| | | 2003-2007* | 1694.3 (1656.3, 1732.4) | -45.5 (-58.1, -32) | -182 (-232.5, -127.8) | -2.7 (-3.4, -1.9) | -10.8 (-13.5, -7.7) |
| | | 2007-2010* | 1511.2 81478.1, 1544.4) | 51.8 (37.3, 65.2) | 207.3 (149, 260.7) | 3.4 (2.4, 4.4) | 13.7 (9.6, 17.4) |
| Men | 50_64 | 2000-2001 | 25.2 (23.3, 27.1) | 0.1 (-0.2, 0.3) | 0.7 (-1.8, 3.2) | 0.3 (-0.6, 1.2) | 2.9 (-6.9, 13.6) |
| | 65_79 | 2000-2001 | 137.2 (129.0, 145.4) | 0.5 (-4.4, 5.5) | 1 (-8.8, 10.9) | 0.4 (-3, 4.2) | 0.7 (-6.1, 8.4) |
| | | 2001-2007* | 138.1 (132.4, 143.9) | -2.1 (-3.2, -1) | -14.9 (-22.7, -7) | -1.5 (-2.3, -0.8) | -10.8 (-16.1, -5.3) |
| | | 2007-2010 | 123.3 (118.3, 128.3) | 1.9 (-0.3, 4.2) | 7.4 (-1.4, 16.9) | 1.5 (-0.3, 3.5) | 6 (-1.1, 13.9) |
| | 80+ | 2000-2003 | 700.2 (660.3, 740.2) | 5.2 (-6.6, 15.6) | 20.7 (-26.6, 62.4) | 0.7 (-0.9, 2.4) | 3 (-3.7, 9.5) |
| | | 2003-2007* | 719.4 (693.2, 745.7) | -8.7 (-15.6, -2.2) | -43.3 (-78.1, -10.9) | -1.2 (-2.1, -0.3) | -6 (-10.5, -1.5) |
| | | 2007-2010* | 676.0 (652.3,699.7) | 15.8 (4.2, 26.6) | 63.1 (16.8, 106.4) | 2.3 (0.6, 4) | 9.3 (2.5, 15.9) |

AgGr – Age Group, AIR – age-specific incidence rates, per 100,000 persons-year, in the beginning of the period, AAC – Annual absolute change, per 100,000 persons-year, PAC – Period absolute change, per 100,000 persons-year, ARC – Annual relative change (%), PRC – Period relative change (%), * p<0.05 for temporal trend (significant change)

## 3.4 Effects Of Climatic Factors On Spatial-temporal Distribution Of Hip Fracture In Portugal

# CLIMATIC EFFECTS ON SPATIAL-TEMPORAL VARIATIONS OF HIP FRACTURE IN PORTUGAL (2000-2010)

**Oliveira CM, Economou T, Trevor B, Carvalho MS, Pina MF**

**Carla Maria Oliveira**

i3S - Instituto de Investigação e Inovação em Saúde, Universidade do Porto, Portugal;

INEB - Instituto de Engenharia Biomédica, Universidade do Porto, Rua do Campo Alegre, 823, 4150-180 Porto, Portugal;

ESTSP/IPP - Escola Superior de Tecnologia da Saúde do Porto, Instituto Politécnico do Porto, Rua Valente Perfeito, 322, 4400-330 Vila Nova de Gaia, Portugal;

FMUP - Departamento de Epidemiologia Clínica, Medicina Preditiva e Saúde Pública da Faculdade de Medicina da Universidade do Porto, Al. Prof. Hernâni Monteiro, 4200 - 319 Porto, Portugal

ISPUP - Instituto de Saúde Pública da Universidade do Porto, Rua das Taipas 135, 4050-600, Porto, Portugal

coliveir@ineb.up.pt

**Theodoros Economou**

College of Engineering, Mathematics and Physical Sciences, University of Exeter, North Park Road, EX4 4QF, Exeter, UK.

t.economou@ex.ac.uk

**Trevor Bailey**

College of Engineering, Mathematics and Physical Sciences, University of Exeter, North Park Road, EX4 4QF, Exeter, UK.

t.c.bailey@ex.ac.uk

**Marília Sá Carvalho**

FIOCRUZ - Fundação Oswaldo Cruz, Av. Brasil, 4365 - Manguinhos, Rio de Janeiro, Brazil.

carvalho@fiocruz.br

**Maria Fátima Pina**

ICICT/FIOCRUZ - Instituto de Comunicação e Informação em Saúde/ Fundação Oswaldo Cruz, Av. Brasil, 4365 - Pavilhão Haity Moussatché - Manguinhos, Rio de Janeiro, CEP: 21040-900,

i3S - Instituto de Investigação e Inovação em Saúde, Universidade do Porto, Portugal;

INEB - Instituto de Engenharia Biomédica, Universidade do Porto, Rua do Campo Alegre, 823, 4150-180 Porto, Portugal;

FMUP - Faculdade de Medicina da Universidade do Porto, Al. Prof. Hernâni Monteiro, 4200 - 319 Porto, Portugal

CARTO-FEN/UERJ - Departamento de Engenharia Cartográfica, Faculdade de Engenharia da Universidade do Estado do Rio de Janeiro. Rua São Francisco Xavier, 524/4ºandar, Maracanã, CEP:20550-900, Rio de Janeiro – RJ, Brazil.

fatima.pina@icict.fiocruz.br

**Corresponding author**: C M Oliveira; coliveira@ineb.up.pt; phone: +351 226074900 ; Fax: +351 226094567; INEB, Instituto de Engenharia Biomédica, Universidade do Porto, Rua do Campo Alegre, 823, 4150-180 Porto, Portugal

**Acknowledgments**: This work had the financial support of Fundação para a Ciência e a Tecnologia FCT / MEC through National Funds within the framework of the project PTDC/SAU-EPI/113424/2009 and co-financed by the FEDER via the PT2020 Partnership Agreement under the 4293 Unit I&D.

We acknowledge the Central Administration of Health Services (ACSS) for the data from the National Hospital Discharge Register.

**Conflict of Interest**: Carla Maria Oliveira, Theodoros Economou, Trevor Bailey, Marilia Sá Carvalho and Maria Fátima Pina declare that they have no conflict of interest.

**Role of funding source**: The funder Fundação para a Ciência e Tecnologia - FCT has no role in this paper.

## ABSTRACT

**BACKGROUND:** Seasonality of hip fracture (HF) may be caused by meteorological factors affecting bone metabolism, muscle strength and falls. Our aim is to identify the effects of climatic factors (CF) on the spatial-temporal distribution of HF admissions in Portugal (2000-2010).

**METHODS:** From the National Hospital Discharge Register we selected admissions of patients aged 50+ with fragility HF (codes 820.x, ICD9.CM). Meteorological data: mean temperature (meanTemp-ºC), precipitation (Prec-mm), relative humidity (RelHum-%) and sunshine duration (SunDur-hours) were obtained from the official institute of meteorology, *"Instituto Português do Mar e da Atmosfera"*. Exposure estimation was performed by a geostatistical procedure: the spatial correlation was characterized by a semivariogram and interpolation was performed using kriging. A Negative Binomial generalized additive model was used to estimate the relative risk (RR) of HF associated with CF changes, adjusting for space, time, seasonality, socioeconomic status, rural condition, and age.

**RESULTS:** We selected 96,905 HF patients, 77.3% being women (these were older than men at admission: mean 81.1±8.5 vs 78.1±10.1 years; p<0.001). No substantial differences in space and time were found in our study after the inclusion of CF; although a differential pattern was observed in seasonality. An inverse association between HF and *SunDur* ($RR_{women}$0.997, $RR_{men}$0.998), *meanTemp* ($RR_{women}$0.943, $RR_{men}$0.957), *PresAtm* ($RR_{women}$0.935, $RR_{men}$0.933) and *Prec* ($RR_{women}$0.922); and a direct association between HF and *HumRel* ($RR_{men}$1.012) was found (not significant for *Prec* in men and for *HumRel* in women).

**CONCLUSIONS:** Meteorological variables seem to explain part of the seasonal effect on HF admissions. These findings may have implications for health management in the context of climate alteration.

**KEYWORD:** Hip fracture, osteoporosis, climate factors, spatial-temporal analysis, spatial epidemiology.

**Introduction:**

Osteoporosis is a major cause of bone fractures in the elderly, especially among women postmenopausal [1]. From all the osteoporotic fractures the most severe are hip fractures (HF) because of the high direct and indirect costs associated with treatment and recovery period, as well as the reduction in the quality of life and an increase in mortality [1]. One of the main causes of osteoporotic HF are low energy impacts caused by falls [2], but this is a complex issue affected by many factors [3]. There is a need to identify factors that affect HF incidence or risk that can reduce at least some of clinical and economic burden [4].

High morbidity and mortality in winter remain an important public health problem caused by the exacerbation of certain diseases. HF is one of the consequences of osteoporosis that contributes to the elevated morbidity and mortality in winter, especially in the elderly [5]. Several studies have evaluated the seasonal changes in HF and the majority reveals an increase HF incidence in winter and a decrease in summer. The differences between summer and winter observed in most of these studies may be caused by meteorological factors that affect bone metabolism and muscle strength. In winter, low sun exposure may decrease the synthesis of vitamin D, which has a direct effect on muscle strength and balance [6] and on the calcium and skeletal homeostasis [7]. The temperature may also, indirectly, contribute to increased bone loss, muscle weakness and bone fragility [8, 9]. Another explanation may be the increased risk of falling in winter due to adverse weather conditions, poor visual acuity caused by reduction in daylight periods [10] and impairment in movement caused by an excess of clothes [11]. Some recent studies pointed latitude and seasonal variation as one explanation for the highest HFs incidence in Scandinavian countries [10].

The aim of this study is to identify the effects of climate factors (CF) on the spatial-temporal distribution of HF admissions from people above 50 years old, at municipality level in Portugal from 2000 to 2010.

## Material and Methods:

### Study area

The study area is Continental Portugal. We excluded from the analysis the two autonomous regions, archipelagos of Azores and Madeira (5% of the Portuguese population) because there were no available data on HF admissions. Continental Portugal is located at southwest of Europe and is bordered on the north and east by Spain and south and west by the North Atlantic Ocean. It has a Mediterranean climate where the annual mean temperature varies from 7 ° C in the mountainous north to 18 ° C in the south [12]. Summers are bland in the highlands of north and the coastal region of the north and center, and autumn/winter are typically windy, rainy and cool [13]. Normally, spring and summer are sunny and temperatures are high during the months of July and August [14]. The country has a mean of 4-6 hours of sunshine in winter and 10-12 hours in summer with higher values in the southeast and lowers in northwest [14]. The mean annual total precipitation is higher in the northern mountains and lower in southern parts of Alentejo [12]. Snow occurs in four districts in the north (Guarda, Bragança, Vila Real and Viseu) and decreases its occurrence towards the south to become non-existent in most of the Algarve [13].

### Data

Data from our population-based observational study were obtained from the National Hospital Discharge Register (NHDR) and include all hospital admissions, from 1 January 2000 to 31 December 2010, of patients aged 50 years and over with a discharge diagnosis of HF (ICD9-CM codes 820.x) caused by traumas of low/moderate energy (ICD9-CM codes E849.0, E849.7 and E880-E888). We excluded readmissions (ICD9-CM codes 996.4 and V54.x) and pathological fractures (ICD9-CM codes 170.x and 171.x). More details regarding NHDR are documented in [15].

We aggregate the number of HF admissions by the municipality of patient residence, admission month, year, sex and 5-year age groups (50-54… 80-84, 85+). The monthly count of HF admissions was adjusted to a 30-day period to eliminate the variation in the number of days in each calendar month.

To calculate the population at-risk we aggregated data per municipality, year, sex and five-year age groups using population data from the 2001 Census and annual official estimates for the other years [16].

The meteorological data from 18 meteorological stations were obtained from *"Instituto Português do Mar e da Atmosfera",* contain daily information such as mean temperature (ºC), precipitation (mm), relative humidity (%), daily amount of sunshine (hours) and atmospheric pressure (hPa) from the 18 districts of Continental Portugal (Figure 1). We aggregate these values by monthly mean for each station to match the HF admissions data. We assumed that individuals were exposed to the weather in the municipality of residence, even if the fracture was treated in a hospital outside their municipality.

The rural classification was obtained from National Institute of Statistics (INE) and socioeconomic characterization of municipalities was obtained on the basis of a set of relevant variables from INE; more detail can be found in [15].

**Statistical analysis**

Spatial interpolation for meteorological exposure values by month and year at locations where no measurements were available was performed by a geostatistical procedure [17]. Assuming an isotropic spatial process, the semi-variogram was calculated for all the point pairs within each distance class and the resultant binned empirical semi-variogram was modeled using the K-Bessel model (also known as the Matern correlation function) thus obtaining an estimate of the semi-variogram[17]. This captures the relationship between spatial dependence and distance of any two points in space. Ordinary Kriging interpolation (spatial prediction) was then used to interpolate the surface of each CF. This is effectively a weighted average of the data, with higher weights attributed to nearby observations compared to ones further away, as governed by the semi-variogram [17]. Kriging is a model-based spatial smoothing technique that is conventionally used to interpolate continuous spatial fields observed at discrete spatial points such as the CF used here.

A negative binomial generalized additive model (GAM) was used to estimate the relative risk (RR) of having an HF associated with variations in CF along with 95% confidence intervals (CIs) for inference. The R package ‘mgcv’ was used to implement the GAM [18]. The possible confounders: age-group, socioeconomic status, and rural conditions were included into the model to allow (possible) different behavior of HF between various categories of age, socioeconomic status and rural conditions. In addition, the centroid of each municipality and the year and month of HF admission occurrence were also included into the model to account for possible spatial and temporal trends in HF admission risk.

Specifically, we assumed that the number of HF admissions, $\mathrm{NFrat}_{\mathrm{imtj}}$, in a specific age group $\mathrm{i} = 1, \dots, 8$, month $\mathrm{m} = 1, \dots, 12$, year $\mathrm{t} = 2000, \dots, 2010$ and municipality $\mathrm{j} = 1, \dots, 278$ is distributed as a negative binomial random variable with mean $\lambda_{\mathrm{imtj}} = \mathrm{NPop}_{\mathrm{itj}}\varrho_{\mathrm{imtj}}$ and a scale parameter $\theta$ to allow for overdispertion (excess variation with respect to a Poisson model). $\mathrm{NPop}_{\mathrm{itj}}$ is the number of people (in units of 100,000) in each i, t and j, and $\varrho_{\mathrm{imtj}}$ is the rate of HF per 100,000 people in each i, m, t and j. For each sex, the parameters of interest were estimated based on the generic model described mathematically as follows:

$$NFrat_{imtj} \sim NegBin(\lambda_{imtj}, \theta)$$

$$\log(\lambda_{\mathrm{imtj}}) = \log(\mathrm{NPop}_{\mathrm{itj}}) + \beta_0 + \beta_1\mathrm{AgGr}_{\mathrm{i}} + \beta_2\mathrm{SES}_{\mathrm{j}} + \beta_3\mathrm{RurUrb}_{\mathrm{j}} +$$

$$\beta_4\mathrm{Month}_{\mathrm{m}} + s_1(\mathrm{Year}^{(t)}) + s_2(Lon^{(j)}, Lat^{(j)}) +$$

$$\beta_5 Prec^{(mtj)} + \beta_6 meanTemp^{(mtj)} + \beta_7 RelHum^{(mtj)} + \beta_8 SunDur^{(mtj)} +$$

$$\beta_9 AtmPres^{(mtj)}$$

where the SES $\left(\mathrm{SES_j}\right)$, the rural condition $\left(\mathrm{RurUrb_j}\right)$ and the centroid $\left(Lon^{(j)}, Lat^{(j)}\right)$ are features of the municipality j. Precipitation $\left(\mathrm{Prec}^{(\mathrm{mtj})}\right)$, mean temperature $\left(\mathrm{meanTemp}^{(\mathrm{mtj})}\right)$, relative humidity $\left(\mathrm{RelHum}^{(\mathrm{mtj})}\right)$, sunshine duration $\left(\mathrm{SunDur}^{(\mathrm{mtj})}\right)$ and atmospheric pressure $\left(\mathrm{AtmPres}^{(\mathrm{mtj})}\right)$ are varying by month $\mathrm{m}$, year $\mathrm{t}$ and municipality j. Let the model above be denoted model2 whereas let model1 be the model without the CF in it, i.e. with $\beta_5 = \beta_6 = \beta_7 = \beta_8 = \beta_9 = 0$.

Non-parametric functions $s_1$ and $s_2$ are one- and two-dimensional smooth functions respectively, to allow for possible nonlinearities in the effects of time (year) and space (centroid municipality) predictors using spline functions (smoothers) [18].

A stepwise forward regression procedure was performed starting with a basic model (model 1) and adding variables one at a time to select a final best model (model 2 with some or all CF). To compare models we used the Akaike Information Criterion (AIC) which is a measure of model fit that penalizes models with too many predictors. The first meteorological candidate variable to include into model 1 was the one that gave the lowest AIC amongst the set of models: model 1 with the addition of a CF. The second inclusion was performed in the same manner, and this procedure was repeated for different meteorological variable until the lowest possible AIC was obtained. Parameter significance for the final model was set to the 5% level.

All statistical analyses were performed using the statistical software R version 2.14.1 (Project for Statistical Computing)[19].

**Results:**

A total of 96,905 admissions, of patients aged 50 years and over, with a discharge diagnosis of HF caused by traumas of low/moderate energy (excluding readmissions and pathological fractures, n=696) were identified in Continental Portugal between 2000 and 2010, after excluding missing code for the municipality of residence (n=585). The affected populations were predominantly women (77.3%). On average, women were older than men at admission (p-value of a Student's t-test <0.001), with a mean age (Standard Deviation – SD) of 81.2 (8.5) versus 78.2 (10.1) years old.

Figure 1 shows the geographic location of the 18 meteorological stations in Portugal.

**Figure 1 – Geographical distribution of the 18 meteorological stations per the 18 district of Continental Portugal**

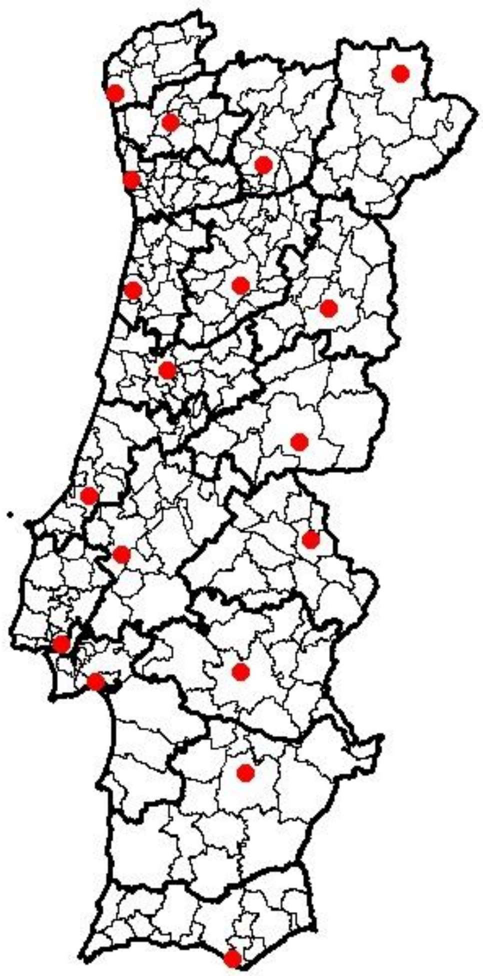
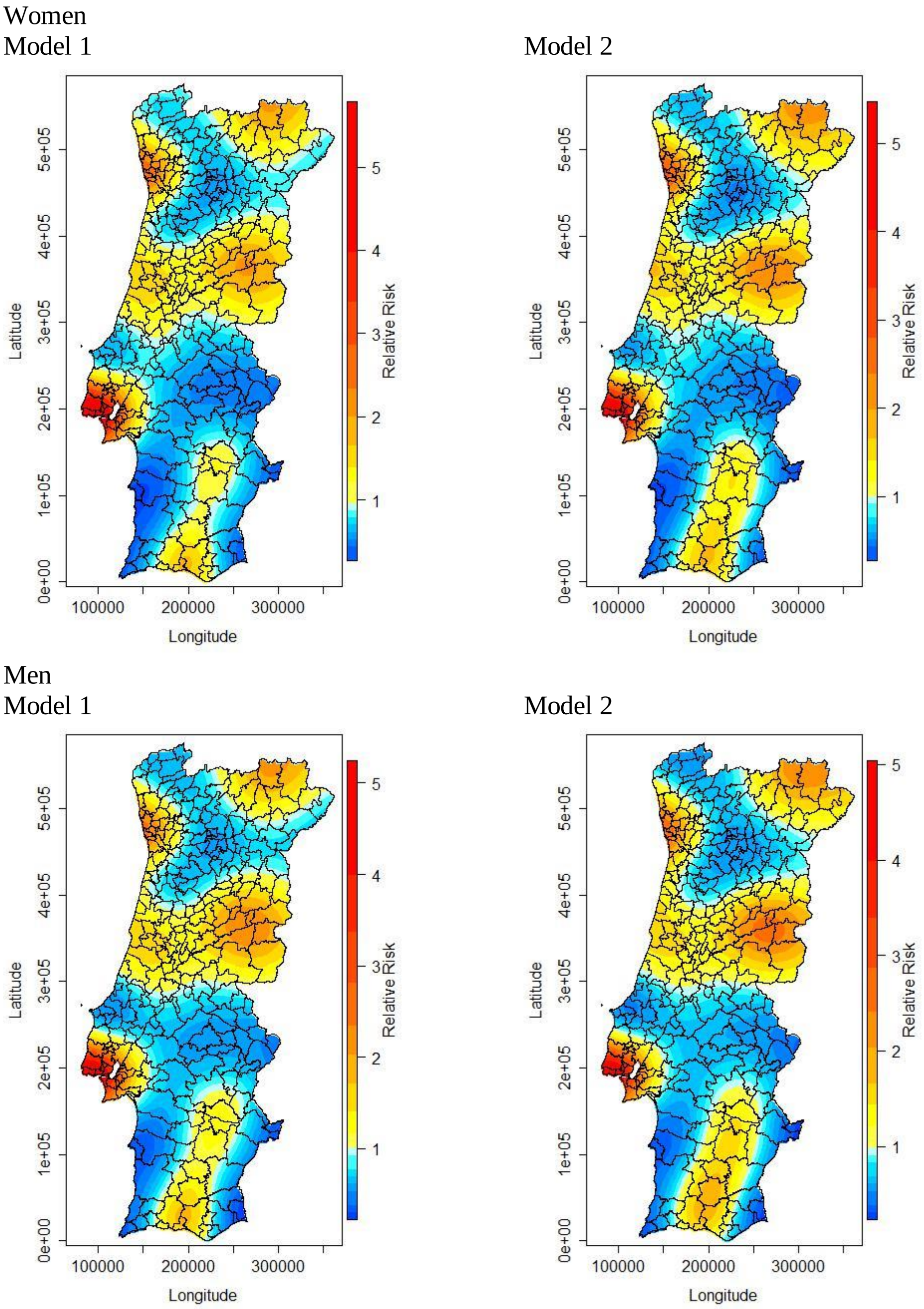


Figure 2 shows the spatial distribution of the RR of HF admission. Only small changes between model 1 and model 2 in the prediction of the spatial distribution of the RR were observed. The meteorological variables seem to not explain much of the spatial variation in HF admission risk.

**Figure 2 – Estimates of the spatial variation of hip fracture risk**



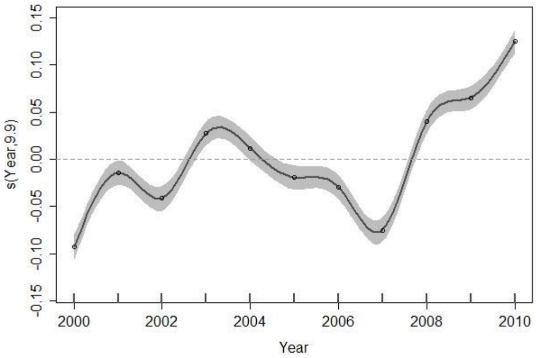

**Model 1:** adjusting for age, regional socioeconomic status and rural condition effects and for seasonality and temporal trend variation
**Model 2:** adjusting for the same covariables as in model-1 and for climatic factors effects effects

No relevant changes between model 1 and model 2 were observed in the temporal trend of HF admissions, in either sex (Figure 3), suggesting that having a some high or low number of incidence of HF admissions in a specific year is not associated with weather characteristics in that particular same year.

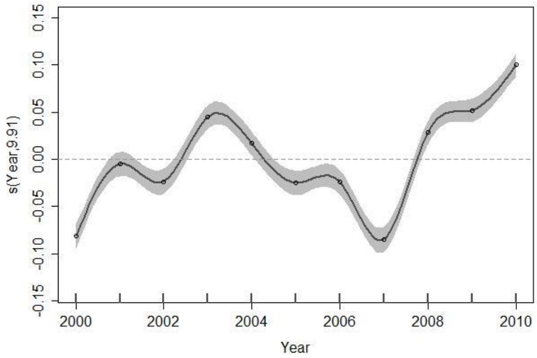
**Figure 3 – Estimates of the temporal trend (2000-2010) variation of hip fracture risk**

Women

Model 1

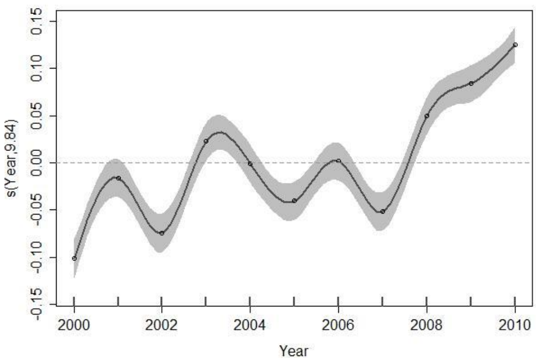



Model 2

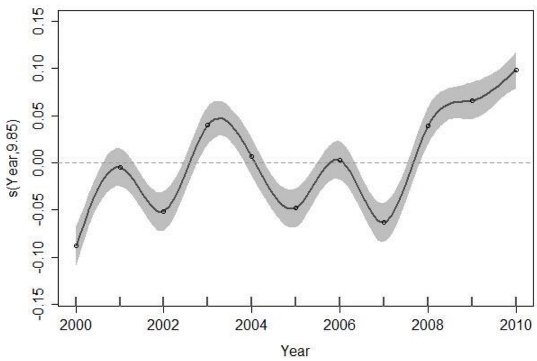



Men

Model 1




Model 2




**Model 1**: adjusting for age, regional socioeconomic status, and rural condition effects and for seasonality and spatial variation
**Model 2**: adjusting for the same covariables as in model-1 and for climatic factors effects

Seasonal variation in HF admission risk was observed in both sexes (Table 1 and Table 2) after adjusting for age group, socioeconomic status, rural conditions, spatial (centroid of municipality) and temporal trend (year) effects (model 1). HF admission was significantly more frequent in winter months than in other months, especially than in summer months in both sexes. However, with the inclusion of CF and comparing model 1 and model 2, it seems that seasonality effects are attenuated in the second model (Figure 4), suggesting that CF might explain part of the seasonality effect.

**Table 1 – Estimates the effect of climate factors and seasonality variation on HF risk in women**

| | | Model 1 | | | Model 2 | | |
|---|---|---|---|---|---|---|---|
| | | RR | Percentage | p-value | RR | Percentage | p-value |
| Month | Jan | 1.194 (1.174, 1.214) | 19.37 (17.42, 21.36) | *** | 1.130 (1.077, 1.185) | 12.97 (7.69, 18.52) | *** |
| | Fev | 1.008 (0.991, 1.025) | 0.76 (-0.94, 2.48) | | 0.939 (0.900, 0.980) | -6.12 (-10.03, -2.04) | * |
| | Mar | 1.073 (1.055, 1.091) | 7.27 (5.48, 9.09) | *** | 1.005 (0.968, 1.043) | 0.51 (-3.18, 4.34) | |
| | Apr | 1.003 (0.986, 1.02) | 0.32 (-1.37, 2.04) | | 0.936 (0.908, 0.965) | -6.39 (-9.22, -3.48) | *** |
| | Mai | 1.008 (0.991, 1.025) | 0.8 (-0.9, 2.52) | | 0.964 (0.941, 0.986) | -3.65 (-5.87, -1.37) | *** |
| | Jun | 0.961 (0.945, 0.978) | -3.86 (-5.5, -2.2) | *** | 0.952 (0.936, 0.969) | -4.75 (-6.39, -3.08) | *** |
| | Jul | 1 | 1 | ---- | 1 | 1 | ---- |
| | Ago | 1.007 (0.99, 1.024) | 0.71 (-0.99, 2.44) | | 1.004 (0.987, 1.022) | 0.41 (-1.33, 2.18) | |
| | Set | 0.965 (0.949, 0.982) | -3.46 (-5.1, -1.79) | *** | 0.959 (0.938, 0.980) | -4.12 (-6.17, -2.03) | *** |
| | Out | 1.062 (1.044, 1.08) | 6.19 (4.42, 8) | *** | 1.051 (1.020, 1.083) | 5.09 (1.97, 8.3) | *** |
| | Nov | 1.106 (1.088, 1.125) | 10.6 (8.76, 12.46) | *** | 1.056 (1.013, 1.101) | 5.6 (1.31, 10.07) | *** |
| | Dec | 1.23 (1.21, 1.25) | 22.96 (20.96, 25) | *** | 1.155 (1.102, 1.211) | 15.51 (10.16, 21.13) | *** |
| Climate factor | Prec (per 10 mm) | | | | 0.922 (0.898, 0.947) | -7.78 (-10.19, -5.3) | *** |
| | meanTemp (per 5°C) | | | | 0.943 (0.930, 0.957) | -5.65 (-6.96, -4.33) | *** |
| | HumRel (per 1 %) | | | | 1.000 (0.994, 1.006) | 0.01 (-0.61, 0.65) | |
| | DurSun (per 1 hour) | | | | 0.997 (0.996, 0.998) | -0.26 (-0.36, -0.16) | *** |
| | AtmPres (per 10 hPa) | | | | 0.935 (0.932, 0.937) | -6.55 (-6.81, -6.29) | *** |
| | AIC | 1803377 | | | 1796529 | | |

‘***’ $p<0.001$ ‘**’ $p<0.01$ ‘*’ $p<0.05$

Model 1: adjusting for age, regional socioeconomic status, and rural condition effects and for temporal trend and spatial variation

Model 2: adjusting for the same covariable as in model-1 and for climatic factors effects

**Table 2 – Estimates the effect of climate factors and seasonality variation on HF risk in men**

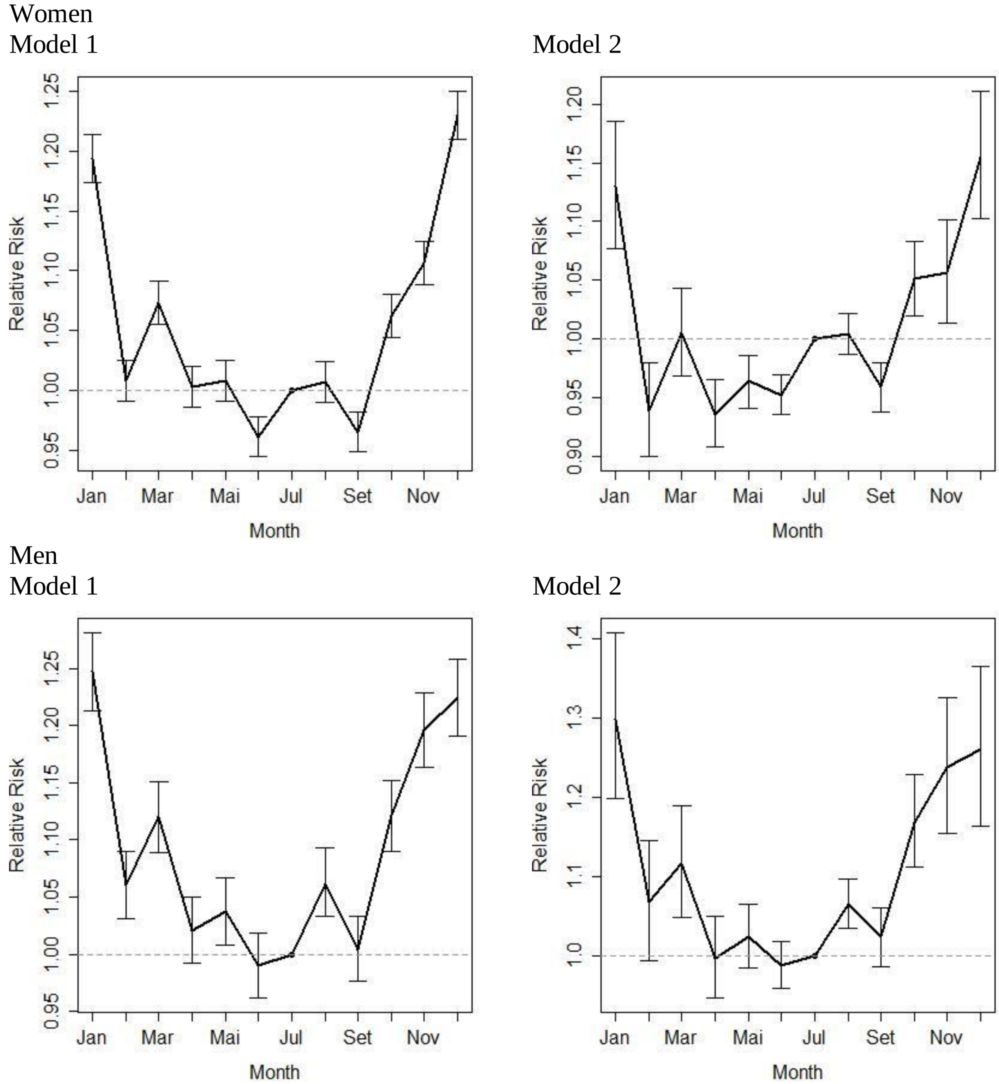
| | | Model 1 | | | Model 2 | | |
|---|---|---|---|---|---|---|---|
| | | RR | Percentage | p-value | RR | Percentage | p-value |
| Month | Jan | 1.247 (1.213, 1.281) | 24.66 (21.31, 28.1) | *** | 1.299 (1.199, 1.407) | 29.9 (19.93, 40.7) | *** |
| | Fev | 1.06 (1.031, 1.09) | 6 (3.05, 9.02) | *** | 1.068 (0.994, 1.146) | 6.76 (-0.56, 14.61) | |
| | Mar | 1.12 (1.089, 1.151) | 11.96 (8.88, 15.12) | *** | 1.117 (1.049, 1.189) | 11.68 (4.93, 18.86) | *** |
| | Apr | 1.021 (0.992, 1.05) | 2.06 (-0.79, 5) | | 0.998 (0.948, 1.051) | -0.18 (-5.15, 5.06) | |
| | Mai | 1.037 (1.008, 1.067) | 3.72 (0.82, 6.69) | * | 1.024 (0.985, 1.065) | 2.44 (-1.48, 6.52) | |
| | Jun | 0.990 (0.962, 1.018) | -1.03 (-3.82, 1.84) | | 0.989 (0.960, 1.018) | -1.11 (-3.96, 1.81) | |
| | Jul | 1 | 1 | ---- | 1 | 1 | ---- |
| | Ago | 1.062 (1.033, 1.093) | 6.23 (3.28, 9.26) | *** | 1.065 (1.035, 1.097) | 6.51 (3.46, 9.65) | *** |
| | Set | 1.004 (0.976, 1.033) | 0.38 (-2.44, 3.28) | | 1.024 (0.987, 1.061) | 2.38 (-1.25, 6.14) | |
| | Out | 1.121 (1.09, 1.152) | 12.07 (8.99, 15.23) | *** | 1.169 (1.112, 1.229) | 16.88 (11.16, 22.9) | *** |
| | Nov | 1.196 (1.163, 1.229) | 19.56 (16.32, 22.9) | *** | 1.238 (1.155, 1.326) | 23.77 (15.51, 32.62) | *** |
| | Dec | 1.224 (1.191, 1.258) | 22.45 (19.15, 25.85) | *** | 1.260 (1.164, 1.364) | 25.97 (16.37, 36.35) | *** |
| Meteo | Prec (per 10 mm) | | | | 0.965 (0.924, 1.008) | -3.47 (-7.6, 0.84) | |
| | meanTemp (per 5°C) | | | | 0.957 (0.935, 0.979) | -4.35 (-6.53, -2.12) | *** |
| | HumRel (per 1 %) | | | | 1.012 (1.001, 1.022) | 1.16 (0.11, 2.22) | * |
| | DurSun (per 1 hour) | | | | 0.998 (0.996, 0.999) | -0.24 (-0.41, -0.07) | ** |
| | AtmPres (per 10 hPa) | | | | 0.933 (0.929, 0.937) | -6.68 (-7.1, -6.26) | *** |
| | AIC | 856253.7 | | | 853786.5 | | |

'***' $p<0.001$ '**' $p<0.01$ '*' $p<0.05$

Model 1: adjusting for age, regional socioeconomic status and rural condition effects and for temporal trend and spatial variation

Model 2: adjusting for the same covariable as in model-1 and for climatic factors effects

**Figure 4 – Estimates of seasonality variation of hip fracture risk**




**Model 1**: adjusting for age, regional socioeconomic status and rural condition effect and for temporal trend and spatial variation
**Model 2**: adjusting for the same covariables as in model-1 and for climatic factors effects

Table 1 and Table 2 shows the effects of CF on HF risk and the effect of age group, SES, rural condition, seasonality, temporal trends (2000-2010) and spatial effects on HF risk before (model 1) and after (model 2) adjusting for CF. Model 2 had a better performance than model 1. Regarding the CF effects, it appears that the direction of the association between men and women are similar. An inverse association between HF and *SunDur*, *meanTemp*, *AtmPres* and *Prec* and a direct association was observed between HF and *HumRel*, however, *Prec* was not significant for men and *HumRel* was not significant for women.

**Discussion:**

The association between CF and HF has been described in previous studies where temperature and sun duration were the main factors [5, 20-22], although it seems that the effect of CF on the spatial distribution of HF is not well described. There was no real consensus regarding the association between climate factor and HF and conflicting evidence was been reported between studies. Our initial hypothesis was that higher incidence of HF in some regions or point in time may be due to the effect of CF. However in our study, CF seems to only explain a small part of the spatial-temporal variations of HF risk in space and time, e.g. part of the seasonal variation in women. Seasonal patterns seem more pronounced in women and the significant "artificial" effects of some months disappear when CF are taken into account for both sexes; suggesting that CF might be related to the higher incidence of HF in winter months and lower incidence in summer months. In our study, it seems that temperature, sun duration and atmospheric pressure reduce HF risk for both sexes, although a direct association between HF and relative humidity seems to be observed in men but not in women and an inverse association between HF and rain seem to be observed in women but not in men.

No substantial differences in space and time variations were found in our study after the inclusion of CF. For instance, Portugal had lower temperatures in the Northeast and also a higher incidence of HF and when we remove the possible effect of temperature on HF risk, a higher HF risk persists to exist in that location (Figure 2). It seems that there are regions-specific characteristics that affect HF independently of the weather. Also, there was no difference in the temporal pattern before and after the CF inclusion, which means that there is no attributed effect of CF on temporal variations of HF; although some difference was observed in the seasonality pattern. Part of the seasonality observed in our study might be attributed to the influence of adverse weather conditions, although it seems to not explain all of the seasonality; probably there are other reasons that influence the seasonality patterns in HF risk.

The majority of the studies reporting the relationship between HF and temperature are in agreement with our findings: an inverse association has been reported in regions like Sydney (Australia) [23], New York City (EU) [21], Montreal (Quebec province, Canada) [24], Taiwan [25]. However, a non-significant association in England [11, 26] and a direct association in the US: HF fracture risk increases per unit increase in mean temperature [5]. This last study tested the interaction between season and climate factors, and a higher mean summer temperature was associated with a significant increase in the risk of HF [5]. The lower temperature might be one of the reasons for the higher incidence of HF in winter presented in the majority of the studies. Colder temperatures may affect the bone metabolism and the lack of coordination increasing the susceptibility to falls, especially in older individuals. Colder temperature might discourage the elderly to participate in outdoor activities and to be more involved in an active lifestyle leading to less physical activity in cold weather resulting in an increase in bone fragility [25]. HF tend to occur more indoors than outdoors [27], however, low temperatures and the lack of suitable house heating may increase the risk of hypothermia which occurs when more heat is lost than the body can produce, leading to lose of ability to move and consequently increase the risk of fall and fracture [28]. The increased risk of trauma at low temperatures can be also attributed to some biological mechanism such as the blood pressure and hemodynamic changes [29] that lead to imbalance. The increase in clothing during the cold weather might also contribute to the loss of movement and impairment increasing the risk of fall and fracture [11].

Studies from New York City (EU) [21], Montreal (Quebec province, Canada) [24] corroborate our findings and show an inverse association between HF and sun duration. However, in Taiwan [25], a non-significant association was found after adjusting for trend, seasonality, and month. The US study [5], investigating the interaction between season and sun intensity, shows that higher sunny summer weather was associated with a significant decrease in the risk of HF. The protective association attributed to the sunshine in the risk of HF may be due to higher serum concentrations of 25-hydroxyvitamin D absorbed by sun exposure [30, 31]. It is shown, by several interventional studies, that increase vitamin D by supplementation improve the bone mineral density [32, 33], reduce the risk of falls [2, 34-36] and fractures [33, 37, 38]. One of the plausible explanations might be the effects of vitamin D on muscle function and inflammation. Vitamin D can improve muscle strength and functional mobility reducing the risk of fall and consequently HF. Vitamin D participated on the immunoregulatory mechanisms that modulate the effects of pro-inflammatory cytokines that have been associated with the increased bone metabolism promoting bone heath. Vitamin D may play an important role of HF risk via different mechanisms [39] that might promote the predisposition to falls, and an increase in bone fragility. The lower visual acuity due to lower hours of sunlight may be also one of the reasons for the higher HF risk in the winter [40].

The relationship between HF and precipitation is not consensual: a direct association between precipitation and HF was shown in regions such as Rochester, Minnesota [41] and Montreal, Canada [22]; a non-significant association was shown in New York City [21] and an indirect association: a decrease in the risk of HF per an increase in precipitation was observed in Taiwan [25] and in Montreal, Canada [4, 24]. Our results showed an inverse association in women but not in men (non-significant association was found in men). Precipitation may play a less important role than temperature since most of the hip fractures occur indoors, and temperature affects individuals even when indoors, unlike [21, 26]. Some studies show that freezing precipitation is also associated with higher incidence of HF [22, 41], although it is also shown that freezing precipitation is also associated with low temperature [22, 41] which might indicate that mean daily temperature might be the most important factor among other climate factors affecting HF. Also, older people during winter rarely go outdoors on inclement days (especially women [22]) and perhaps this may be one of the reasons for the protective effects of precipitation in women and the non-significant effect in men find in our study; since precipitation will affect more outside activities.

Studies from New York City [21], Spain [42], Taiwan [43] show a non-significant association between HF and humidity. Our results showed direct association in men but not in women (non-significant association was found in women). This can be because older men are more likely to go out in inclement days than older women [22] and probably they are more at higher risk to suffer a hip fracture in humid months.

Only a small number of studies report the association between HF and atmospheric pressure and conflicting results were found. A study in Spain showed a direct association between mean atmospheric pressure and HF; in Taiwan [25] a non-significant association was found after adjusting for trend, seasonality, and month – however, our study showed an inverse association. The mechanisms that can explain the relation between atmospheric pressure and HF was not found in literature, although some studies relating the effect of CF on rheumatic diseases show an increase in rheumatic symptoms, such as pain joint, with a decrease in atmospheric pressure [44]. The biological mechanism of pressure-symptom association might be that intra-articular pressure is normally lower than atmospheric pressure and when pressure decreases and equals the intra-articular pressure, may lead to a subluxation of the hip joint that influence arthritis symptoms [45] such as inflammation and pain. That may explain why a decrease in atmospheric pressure might lead to an increase in the risk of falls, especially in the elderly observed in our study.

Some studies, investigate the influence of other climatic factors and identify an increase in HF occurrence in days with snow in regions like Norway (Stavanger, Trondheim, and Harstad) [9], Montreal, Canada [4, 24] and Taiwan [25]. However, a non-significant association was observed in New York City (EU) [21]. Portugal is not a country greatly affected by snow and regarding this aspect, no sufficient information was available to analysis this effect.

One possible limitation of the study is that data are provided by the NHDR that does not cover private hospitals, although due to the high cost involved and to the universal and tendentiously free-of-charge of the national health-care system, almost all of HF is treated in the public health system. Another limitation of our study is the possible misclassification of the exposure. We assume that individuals are exposed to the weather of the municipality of their residence and this might not represent the actual experience of individuals. Individuals can work in another municipality and be also exposed to the weather of the municipality of their work. However, this misclassification is not systematic; it is random, which minimizes the potential bias. We consider that such limitation had a lower impact on bias in our results since there is no reason to believe that this experience on exposure will be systematic and would differ among geographic areas. Also, a more dense meteorological data are required to have more precision on the climate factors estimates. This is an ecological study so conclusions must be taken with caution and also, it did not control for some possible confounder factor such as individuals' socioeconomic status. Also, it is not possible to identify indoors or outdoors fractures and since the majority of HF occurs inside the house, the results may be slightly biased.

The strengths of our study are the large-scale population-based design that allows a sample statistical power and the longitudinal data from nationwide registers that minimize the risk of selection and information bias.

**Conclusions:**

This study showed that meteorological variables seem to explain part of the seasonal effect on HF risk and these findings may have an implication on the health management in the context of prevention HF. However, it seems not to explain much of the spatial and annually temporal pattern. The consistency pattern of HF after adjusted for meteorological variables suggest that factors other than regional weather may be linked to a spatial and temporal pattern of HF incidence. More studies needed to elucidate the factors associated with differences in space and time to allow more effective strategies of prevention.

**References**

1. NIH Consensus Development Panel on Osteoporosis Prevention, Diagnosis, and Therapy, March 7-29, 2000: highlights of the conference. South Med J. 2001;94(6):569-73. Epub 2001/07/07.

2. Bischoff HA, Stahelin HB, Dick W, Akos R, Knecht M, Salis C, et al. Effects of vitamin D and calcium supplementation on falls: a randomized controlled trial. Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research. 2003;18(2):343-51. Epub 2003/02/06.

3. Wareham K, Johansen A, Stone MD, Saunders J, Jones S, Lyons RA. Seasonal variation in the incidence of wrist and forearm fractures, and its consequences. Injury. 2003;34(3):219-22. Epub 2003/03/08.

4. Modarres R, Ouarda TB, Vanasse A, Orzanco MG, Gosselin P. Modeling climate effects on hip fracture rate by the multivariate GARCH model in Montreal region, Canada. International journal of biometeorology. 2014;58(5):921-30. Epub 2013/06/01.

5. Bischoff-Ferrari HA, Orav JE, Barrett JA, Baron JA. Effect of seasonality and weather on fracture risk in individuals 65 years and older. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA. 2007;18(9):1225-33. Epub 2007/03/27.

6. Muir SW, Montero-Odasso M. Effect of vitamin D supplementation on muscle strength, gait and balance in older adults: a systematic review and meta-analysis. Journal of the American Geriatrics Society. 2011;59(12):2291-300. Epub 2011/12/23.

7. Anderson PH, Turner AG, Morris HA. Vitamin D actions to regulate calcium and skeletal homeostasis. Clin Biochem. 2012. Epub 2012/03/15.

8. Tucker P, Gilliland J. The effect of season and weather on physical activity: a systematic review. Public Health. 2007;121(12):909-22. Epub 2007/10/09.

9. Bulajic-Kopjar M. Seasonal variations in incidence of fractures among elderly people. Injury prevention : journal of the International Society for Child and Adolescent Injury Prevention. 2000;6(1):16-9. Epub 2000/03/23.

10. Tenias JM, Estarlich M, Fuentes-Leonarte V, Iniguez C, Ballester F. Short-term relationship between meteorological variables and hip fractures: an analysis carried out in a health area of the Autonomous Region of Valencia, Spain (1996-2005). Bone. 2009;45(4):794-8. Epub 2009/07/01.

11. Chesser TJ, Howlett I, Ward AJ, Pounsford JC. The influence of outside temperature and season on the incidence of hip fractures in patients over the age of 65. Age and ageing. 2002;31(5):343-8. Epub 2002/09/21.

12. IPMAR. Clima de Portugal Continental Instituto de Meteorologia (1961–1990) - Área Educativa - Clima em Portugal. Instituto de Meteorologia. . Instituto de Meteorologia; [cited 2015 15-11-2014]; Available from: http://www.webcitation.org/643jP1kDD.

13. Rodrigues A. Novas Viagens — O Meio Natural. 1.º ed2004.

14. Portugal-Virtual. Clima de Portugal Portugal — Clima. [15-12-2014]; Available from: http://www.webcitation.org/643jS4VIb.

15. Alves SM, Castiglione D, Oliveira CM, de Sousa B, Pina MF. Age-period-cohort effects in the incidence of hip fractures: political and economic events are

coincident with changes in risk. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA. 2014;25(2):711-20. Epub 2013/08/29.

16. INE. *Instituto Nacional de Estatística*; [cited 2012]; Available from: www.ine.pt.

17. Diggle P, Ribeiro PJ. Model-based Geostatistics: Springer; 2007.

18. Wood SN. Generalized Additive Models: An Introduction with R. . Press CaHC, editor2006.

19. R-Core-Team. R: A language and environment for statistical computing. Vienna, Austria2014.

20. Koren L, Barak A, Norman D, Sachs O, Peled E. Effect of seasonality, weather and holidays on the incidence of proximal hip fracture. The Israel Medical Association journal : IMAJ. 2014;16(5):299-302. Epub 2014/07/02.

21. Mirchandani S, Aharonoff GB, Hiebert R, Capla EL, Zuckerman JD, Koval KJ. The effects of weather and seasonality on hip fracture incidence in older adults. Orthopedics. 2005;28(2):149-55. Epub 2005/03/09.

22. Levy AR, Bensimon DR, Mayo NE, Leighton HG. Inclement weather and the risk of hip fracture. Epidemiology. 1998;9(2):172-7. Epub 1998/03/21.

23. Lau EM, Gillespie BG, Valenti L, O'Connell D. The seasonality of hip fracture and its relationship with weather conditions in New South Wales. Australian journal of public health. 1995;19(1):76-80. Epub 1995/02/01.

24. Modarres R, Ouarda TB, Vanasse A, Orzanco MG, Gosselin P. Modeling seasonal variation of hip fracture in Montreal, Canada. Bone. 2012;50(4):909-16. Epub 2012/01/25.

25. Lin HC, Xirasagar S. Seasonality of hip fractures and estimates of season-attributable effects: a multivariate ARIMA analysis of population-based data. Osteoporosis International. 2006;17(6):795-806.

26. Bastow MD, Rawlings J, Allison SP. Undernutrition, hypothermia, and injury in elderly women with fractured femur: an injury response to altered metabolism? Lancet. 1983;1(8317):143-6. Epub 1983/01/22.

27. Keegan TH, Kelsey JL, King AC, Quesenberry CP, Jr., Sidney S. Characteristics of fallers who fracture at the foot, distal forearm, proximal humerus, pelvis, and shaft of the tibia/fibula compared with fallers who do not fracture. American journal of epidemiology. 2004;159(2):192-203. Epub 2004/01/14.

28. Campbell AJ, Spears GF, Borrie MJ, Fitzgerald JL. Falls, elderly women and the cold. Gerontology. 1988;34(4):205-8. Epub 1988/01/01.

29. Collins KJ, Easton JC, Belfield-Smith H, Exton-Smith AN, Pluck RA. Effects of age on body temperature and blood pressure in cold environments. Clin Sci (Lond). 1985;69(4):465-70. Epub 1985/10/01.

30. Diffey BL. Modelling vitamin D status due to oral intake and sun exposure in an adult British population. The British journal of nutrition. 2013;110(3):569-77. Epub 2013/01/24.

31. Harris SS, Dawson-Hughes B. Seasonal changes in plasma 25-hydroxyvitamin D concentrations of young American black and white women. The American journal of clinical nutrition. 1998;67(6):1232-6. Epub 1998/06/13.

32. Reid IR, Bolland MJ. Skeletal and nonskeletal effects of vitamin D: is vitamin D a tonic for bone and other tissues? Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA. 2014;25(10):2347-57. Epub 2014/05/23.

33. Dawson-Hughes B, Harris SS, Krall EA, Dallal GE. Effect of calcium and vitamin D supplementation on bone density in men and women 65 years of age or older. The New England journal of medicine. 1997;337(10):670-6. Epub 1997/09/04.

34. Pfeifer M, Begerow B, Minne HW, Suppan K, Fahrleitner-Pammer A, Dobnig H. Effects of a long-term vitamin D and calcium supplementation on falls and parameters of muscle function in community-dwelling older individuals. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA. 2009;20(2):315-22. Epub 2008/07/17.

35. Larsen ER, Mosekilde L, Foldspang A. Vitamin D and calcium supplementation prevents severe falls in elderly community-dwelling women: a pragmatic population-based 3-year intervention study. Aging clinical and experimental research. 2005;17(2):125-32. Epub 2005/06/28.

36. Bischoff-Ferrari HA, Dawson-Hughes B, Willett WC, Staehelin HB, Bazemore MG, Zee RY, et al. Effect of Vitamin D on falls: a meta-analysis. JAMA. 2004;291(16):1999-2006. Epub 2004/04/29.

37. Sahni S, Hannan MT, Gagnon D, Blumberg J, Cupples LA, Kiel DP, et al. Protective effect of total and supplemental vitamin C intake on the risk of hip fracture--a 17-year follow-up from the Framingham Osteoporosis Study. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA. 2009;20(11):1853-61. Epub 2009/04/07.

38. Rossini M, Alberti V, Flor L, Masiero L, Giannini S, Gatti D, et al. Effect of oral vitamin D2 yearly bolus on hip fracture risk in elderly women: a community primary prevention study. Aging clinical and experimental research. 2004;16(6):432-6. Epub 2005/03/03.

39. Laird E, Ward M, McSorley E, Strain JJ, Wallace J. Vitamin D and bone health: potential mechanisms. Nutrients. 2010;2(7):693-724. Epub 2010/07/01.

40. Reed-Jones RJ, Solis GR, Lawson KA, Loya AM, Cude-Islas D, Berger CS. Vision and falls: a multidisciplinary review of the contributions of visual impairment to falls among older adults. Maturitas. 2013;75(1):22-8. Epub 2013/02/26.

41. Jacobsen SJ, Sargent DJ, Atkinson EJ, O'Fallon WM, Melton LJ, 3rd. Population-based study of the contribution of weather to hip fracture seasonality. American journal of epidemiology. 1995;141(1):79-83. Epub 1995/01/01.

42. Tenias JM, Estarlich M, Crespo E, Roman-Ortiz C, Arias-Arias A, Ballester F. Short-term relationship between hip fracture and weather conditions in two Spanish health areas with different climates. Journal of environmental and public health. 2015;2015:395262. Epub 2015/03/12.

43. Lin HC, Xiraxagar S. Seasonality of hip fractures and estimates of season-attributable effects: a multivariate ARIMA analysis of population-based data. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA. 2006;17(6):795-806. Epub 2006/02/24.

44. Verges J, Montell E, Tomas E, Cumelles G, Castaneda G, Marti N, et al. Weather conditions can influence rheumatic diseases. Proceedings of the Western Pharmacology Society. 2004;47:134-6. Epub 2005/01/07.

45. Wingstrand H, Wingstrand A, Krantz P. Intracapsular and atmospheric pressure in the dynamics and stability of the hip. A biomechanical study. Acta orthopaedica Scandinavica. 1990;61(3):231-5. Epub 1990/06/01.

## 3.5 Regional drinking water composition effects on hip fracture risk. A spatial analysis of nationwide hospital admissions from 2000 to 2010

# REGIONAL DRINKING WATER COMPOSITION EFFECTS ON HIP FRACTURE RISK. A SPATIAL ANALYSIS OF NATIONWIDE HOSPITAL ADMISSIONS FROM 2000 TO 2010

**Oliveira CM, Alves SM, Teixeira H, Economou T,**

**Pereira-da-Silva J, Bailey T, Pina MF**

**Carla Maria Oliveira**

i3S - Instituto de Investigação e Inovação em Saúde, Universidade do Porto, Portugal;

INEB - Instituto de Engenharia Biomédica, Universidade do Porto, Rua do Campo Alegre, 823, 4150-180 Porto, Portugal;

ESTSP/IPP - Escola Superior de Tecnologia da Saúde do Porto, Instituto Politécnico do Porto, Rua Valente Perfeito, 322, 4400-330 Vila Nova de Gaia, Portugal;

FMUP - Departamento de Epidemiologia Clínica, Medicina Preditiva e Saúde Pública da Faculdade de Medicina da Universidade do Porto, Al. Prof. Hernâni Monteiro, 4200 - 319 Porto, Portugal

ISPUP - Instituto de Saúde Pública da Universidade do Porto, Rua das Taipas 135, 4050-600, Porto, Portugal

coliveir@ineb.up.pt

**Sandra Maria Alves**

i3S - Instituto de Investigação e Inovação em Saúde, Universidade do Porto, Portugal;

INEB - Instituto de Engenharia Biomédica, Universidade do Porto, Rua do Campo Alegre, 823, 4150-180 Porto, Portugal;

ESTSP/IPP, Escola Superior de Tecnologia da Saúde do Porto, Instituto Politécnico do Porto, Rua Valente Perfeito, 322, 4400-330 Vila Nova de Gaia, Portugal;

smfa@ineb.up.pt

**Hugo Teixeira**

i3S - Instituto de Investigação e Inovação em Saúde, Universidade do Porto, Portugal;

INEB - Instituto de Engenharia Biomédica, Universidade do Porto, Rua do Campo Alegre, 823, 4150-180 Porto, Portugal;

hugo.teixeira@ineb.up.pt

**Theodoros Economou**

College of Engineering, Mathematics and Physical Sciences, University of Exeter, North Park Road, EX4 4QF, Exeter, UK.

t.economou@ex.ac.uk

**José Pereira da Silva**

Clínica Universitária de Reumatologia. Faculdade de Medicina e Centro Hospitalar e Universitário de Coimbra. Portugal

jdasilva@ci.uc.pt

**Trevor Bailey**

College of Engineering, Mathematics and Physical Sciences, University of Exeter, North Park Road, EX4 4QF, Exeter, UK.

t.c.bailey@ex.ac.uk

**Maria Fátima Pina**

ICICT/FIOCRUZ - Instituto de Comunicação e Informação em Saúde/ Fundação Oswaldo Cruz, Av. Brasil, 4365 - Pavilhão Haity Moussatché - Manguinhos, Rio de Janeiro, CEP: 21040-900,

i3S - Instituto de Investigação e Inovação em Saúde, Universidade do Porto, Portugal;

INEB - Instituto de Engenharia Biomédica, Universidade do Porto, Rua do Campo Alegre, 823, 4150-180 Porto, Portugal;

FMUP - Faculdade de Medicina da Universidade do Porto, Al. Prof. Hernâni Monteiro, 4200 - 319 Porto, Portugal

CARTO-FEN/UERJ - Departamento de Engenharia Cartográfica, Faculdade de Engenharia da Universidade do Estado do Rio de Janeiro. Rua São Francisco Xavier, 524/4ºandar, Maracanã, CEP:20550-900, Rio de Janeiro – RJ, Brazil.

fatima.pina@icict.fiocruz.br

**Corresponding author**: C M Oliveira; coliveira@ineb.up.pt; phone: +351 226074900 ; Fax: +351 226094567; INEB, Instituto de Engenharia Biomédica, Universidade do Porto, Rua do Campo Alegre, 823, 4150-180 Porto, Portugal

**Acknowledgments**: This work had the financial support of Fundação para a Ciência e a Tecnologia FCT / MEC through National Funds within the framework of the project PTDC/SAU-EPI/113424/2009 and co-financed by the FEDER via the PT2020 Partnership Agreement under the 4293 Unit I&D.

We acknowledge the Central Administration of Health Services (ACSS) for the data from the National Hospital Discharge Register.

**Conflict of Interest**: Carla Maria Oliveira, Sandra Maria Alves, Hugo Teixeira, Theodoros Economou, José Pereira da Silva, Trevor Bailey and Maria Fátima Pina declare that they have no conflict of interest.

**Role of funding source**: The funder Fundação para a Ciência e Tecnologia - FCT has no role in this paper.

## ABSTRACT

**INTRODUCTION: A g**eographical variation on hip fractures (HF) may be related to the geographical variation of drinking water composition (DWC); minerals in drinking water can lead to deposition of minerals in bones contributing to its fragility. We aim to investigate the effects of DWC on HF risk in Portugal (2000-2010).

**METHODS:** From National Hospital Discharge Register we selected admissions of patients aged ≥50 years, with a diagnosis of HF caused by low/moderate energy traumas. Water components (aluminum, cadmium, calcium, fluoride, iron, magnesium, manganese) and characteristics (pH and color) were selected at the municipality level. A spatial negative binomial generalized additive model was used to estimate the association of HF with variation in DWC (adjusted for sex, age group, socioeconomic status, rural condition and spatial trends).

**RESULTS**: There were 96,905 HF (77.3% in women). On average, women were older than men (81.1±8.5 vs 78.1±10.1 years; p<0.001). The spatial pattern of HF risk was attenuated after adjusted for water parameters. Results show an indirect association between calcium, magnesium and iron and HF risk but no clear relation between aluminum, cadmium, fluoride, manganese or color and HF risk. Regarding pH, it seems that between 6.7 and 7 pH there is a lower risk than in more basic water (>7) and between 6.5-6.7.

**CONCLUSIONS:** Different dose-response relationships were identified. The increase of calcium, magnesium and iron values in DWC seems to reduce the HF risk. Long-term exposure to water parameters, even within the regulatory limits, might increase the risk of HF. Our study contributes to a better understand of the role drinking water in the HF risk.


**KEYWORD:** Hip fracture, drinking water composition, hospital admissions, spatial epidemiology.

## Introduction

Osteoporosis is a condition characterized by a low bone mineral density that increases bone fragility and consequently the susceptibility to suffer fractures [1]. Hip fractures (HF) are the most severe osteoporotic fractures because require surgical treatment followed by a long recovery period [2] with high costs to health care systems, society and families [3]. The risk of osteoporosis, and consequently of HF, increases exponentially with age and it is higher among women, mainly because of an intense loss of bone mass after the menopause. With the worldwide increasing longevity, the number of HF is also increasing, although the incidence rates (a risk measure) vary widely between and within countries [4]. Generally, in the north hemisphere, regions with lower latitude have a lower incidence rate of HF and regions with higher latitude have higher incidence rates, especially Scandinavian regions [5, 6]. Portugal is an intermediate risk country for HF, with overall incidence rates lower than in the USA and in the northern European countries and higher than in some Asian and other Southern European countries [5, 7]. However, there is a large variation within Portugal, with marked geographical patterns and spatial clusters of high and low incidence, showing that there is a spatial dependency in the incidence of HF. The rate ratio (highest versus lowest HF incidence rates) in Portugal is over three times [8] and higher risk municipalities present HF incidence rates comparable with some Scandinavia countries [5, 6, 8]. The underlying causes of HF are multifactorial and although individual factors such as nutrition and physical activity play an important role [9, 10], environmental and socioeconomic factors should not be disregard. In Portugal, the socioeconomic inequalities explain only a small part of the high spatial variability in HF risk [11]. The role of environmental factors in HF risk is still not clear, especially in respect to long-term daily exposure to low doses of minerals or heavy metals by ingestion (drinking or eating) or inhalation (breathing) that can have an impact on health [12]. The mineral composition of water is among the environmental factors that seem to be associated with osteoporosis [13-15] and, therefore, long-term exposure to drinking water might be one possible reason for the geographical variation of HF incidence [16] although studies are still sparse and inconsistent [17]. Depending on the dose of some components of the water, such as aluminum or cadmium, seem to deteriorate bone health while others, such as calcium, magnesium, and manganese seem to protect bone health [18]. The deposition of such minerals and metals (even in low doses) in bones, as a result of long-term exposures, might contribute to the fragility (e.g. aluminum) or to the resistance (e.g. magnesium and calcium) of bones [1]. The beneficial effect of calcium on the bone mineral density is higher when calcium is in the presence of vitamin D rather than calcium alone [19] and this might be because vitamin D increases the calcium absorption helping to maintain the levels of parathyroid hormone (PTH) within the physiological limits [20]. Iron deficiency led to a delay in collagen maturation in the femoral bones and to phosphorus-calcium metabolic disorders [21]; magnesium is associated with regulation of calcium transport [22] and manganese can activate enzymes involved in bone metabolism [23], which can therefore, explain the protective effect of these elements. Aluminum is associated with the reduction of osteoblast activity [24] and cadmium may affect calcium metabolism [25], which may be possible reasons for the detrimental effect of both elements in the bone health. Inconsistency results have been reported regarding the effect of fluoride on the bone, suggesting that lower levels might be beneficial to bone quality by increasing the density of trabecular bone [26] and by stimulating osteoblasts and inhibiting osteoclasts while higher levels might have a toxic effect [20]. Water characteristics such as color or pH may also affect the bone health: higher color grades may indicate a high presence of organic matter, which promotes growth opportunities for microorganism and reduces the effectiveness of water disinfection [17]. Besides, pH interfere in the toxicity of metals in water as it regulates most chemical retains [27] and higher color grades are related to acid (pH less than 7) and soft (low concentration of minerals) waters that usually have a harmful effect on bone heath [17].

Exposure to water components does not occur only by drinking the water consumption but also by using the water to prepare the food. Food cooked in water deficient in minerals becomes poorest in terms of that minerals than the food cooked in water rich in minerals, such as magnesium [28].

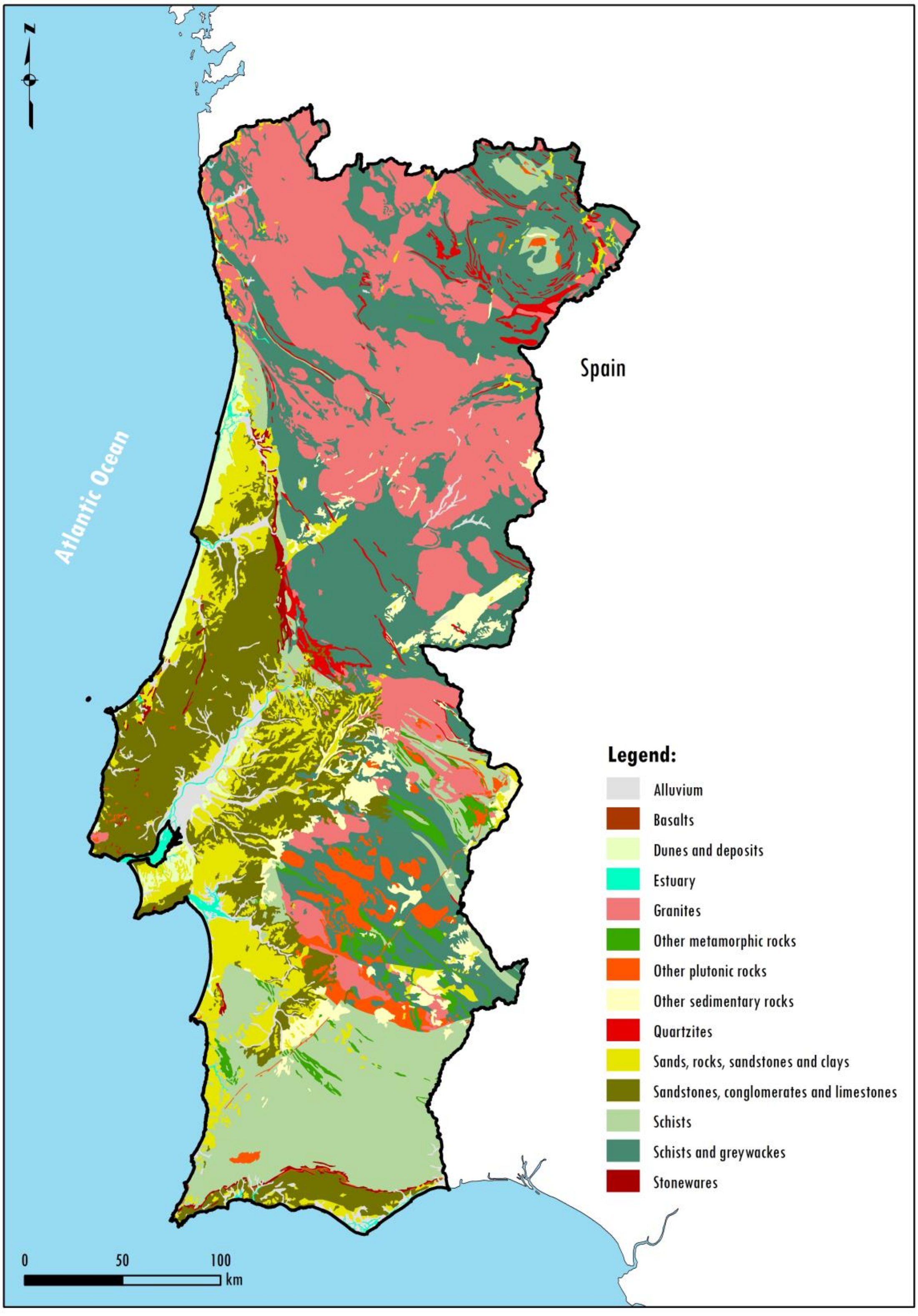
Distinctive regional geological conditions in Portugal [29] lead to differences in the composition of municipal drinking water, and this might be one possible explanation for the high spatial variation in HF risk. Our aim is, therefore, to investigate the effects of municipality drinking water composition (DWC) on the risk of HF among inpatients aged 50 and older in Portugal, from 2000 to 2010.

## Material and Methods

### Study area

The study area is Portugal excluding the two autonomous regions, archipelagos of Azores and Madeira (5% of the Portuguese population) because there were no available data on hospital admissions for those regions. Portugal is one of the most aged countries in Europe27: in 2010 it was the fifth country in the ranking of the higher percentage of persons aged 65 and over [30], with an ageing index of 120 elderly (≥65 years-old) per 100 youths (≤14 years-old) and 37.7% of the population older than 50 years (INE - Statistics Portugal [31] ). Recent demographic trends point to a continuous increase in life expectancy, increasing emigration and decreasing in fertility rates in Portugal, therefore raising the population aging index [31]. Continental Portugal had 10,057,999 inhabitants in 2010, distributed heterogeneously throughout 278 municipalities – the least populated municipality has 1,836 inhabitants, and the most, the capital, has 548,422 inhabitants. The public water supply service is administrated by municipal and private companies to almost all (over 95%) households [32]. The DWC is influenced by the lithology of the soil which, in the continental territory, has three main groups: the acid rocks, predominant in the north region, contribute to a low mineralization of the water [33]; the basic rocks, predominant in the Alentejo region, contribute to medium mineralization of the water; and the sedimentary rocks, located mainly along the sedimentary basin of the Tejo River and the Algarve region, contribute to a high mineralization of the water (Figure 1) [33]. The DWC differs greatly from region to region being more calcareous and consequently with higher hardness and conductivity in the south of the country [34]. The quality of the drinking water for human consumption in Portugal is considered excellent in almost all the territory [29].

**Figure 1 – Geographic distribution of lithology of the soil in Continental Portugal**



## Data

This is an observational population-based ecological study using secondary data from the Portuguese National Hospital Discharge Register (NHDR). From the NHDR, we selected all hospital admissions of patients aged 50 years or over with a discharge diagnosis of HF (ICD9-CM codes 820.x) caused by traumas of low/moderate energy (ICD9-CM codes E849.0, E849.7 and E880-E888), from 1 January 2000 to 31 December 2010. Readmissions for aftercare (ICD9-CM codes 996.4 and V54.x) and pathological fractures (ICD9-CM codes 170.x and 171.x) were excluded. More information on the NHDR can be found elsewhere [35], but briefly, since 2000 NHDR is a compulsory system for all the public hospitals, and contains demographic and clinical data of patients – each register corresponds to one discharge. We aggregated data by the municipality of patient's residence, admission year, sex and 5-year age groups (50-54,… 80-84, 85+). The same age groups were used to aggregate counts of population, by sex and municipality. We used official population data from the Statistics Portugal (INE) - census data for the year 2001 and annual official estimates for the inter-census years [31].

Physical and chemical parameters of municipality DWC were obtained from the Regulatory Authority of Water and Waste Services (Entidade Reguladora dos Serviços de Água e Resíduos) [32]. DWC data were available by the municipality for 2011 and 2012, and values correspond to the median of one-year samples, for each component. We considered the mean values of the two available years. The decision of water components to be included in the analysis was based on its potential relation to bone health, according to literature review [12, 19, 20, 36-40]; we included aluminum, cadmium, calcium, fluoride, iron, magnesium and manganese. Additionally, we also included in the analysis proprieties of the drinking water, such as color or pH. The censored values were set at the highest detection limit values (e.g., <0.01 µg/l became 0.01 µg/l).

We considered land occupation for each municipality according to the classification suggested by Statistics Portugal: rural, urban, and semi-urban. Socioeconomic characterization of municipalities was calculated by principal component analysis based on a set of variables from the 2001 Census, followed by hierarchical cluster analysis;

more detail about the method can be found elsewhere [11].

**Statistical analysis**

A spatial negative binomial generalized additive model was used to estimate the relative risk (RR) of HF associated with variation in DWC, and the corresponding 95% confidence intervals (CIs). Age group, socioeconomic status, and rural conditions were included into the model to allow (possible) different behavior of HF between the various categories. In addition, the centroid (geometric center) coordinates of each municipality and the year of HF occurrence were also included in the model to account for possible spatial and time trends in HF risk.

We assumed that the number of HF, $\mathrm{NFrat_{sijt}}$, in a specific sex $\mathrm{s} = 1{,}2$, age group $\mathrm{i} = 1, \ldots, 8$, municipality $\mathrm{j} = 1, \ldots, 278$ and year $\mathrm{t} = 2000, \ldots, 2010$ is distributed as a negative binomial random variable with mean $\lambda_{\mathrm{sijt}} = \mathrm{NPop_{sijt}}\varrho_{\mathrm{sijt}}$ and a scale parameter $\theta$ to allow for overdispersion (excess variation with respect to a Poisson model). $\mathrm{NPop_{sijt}}$ is the population (in unit of 100,000) in each sex s, age group i, municipality j, and year t and $\varrho_{\mathrm{sijt}}$ is the rate of HF per 100,000 population in each sex s, age group i, municipality j, and year $\mathrm{t}$. The parameters of interest were estimated based on the following complete model or in a subset of the complete model as reveal appropriate:

$NFrat_{itj} \sim NegBin(\lambda_{ijt}, \theta)$

$$log(\lambda_{sijt}) = log(NPop_{sijt}) + \beta_0 + \beta_2 Sex_s + \beta_3 AgGr_i$$

$$+\beta_4 SES_j + \beta_5 RurUrb_j +$$

$$+s_1(Year^{(t)}) + s_2(Lon^{(j)}, Lat^{(j)})$$

$$+s_1(Alum^{(j)}) + s_1(Cad^{(j)}) + s_1(Cal^{(j)}) +$$

$$+s_1(Cor^{(j)}) + s_1(Flu^{(j)}) + s_1(Iron^{(j)})$$

$$+s_1(Magn^{(j)}) + s_1(Mang^{(j)}) + s_1(pH^{(j)})$$

where the SES $\left(\mathrm{SES_j}\right)$, the rural condition $\left(\mathrm{RurUrb_j}\right)$, the centroid $\left(Lon^{(j)}, Lat^{(j)}\right)$ and water components such as aluminum $(Alum^{(j)})$, cadmium $(Cad^{(j)})$, calcium $(Cal^{(j)})$, , fluoride $(Flu^{(j)})$, iron $(Iron^{(j)})$, magnesium $\left(Magn^{(j)}\right)$, manganese $\left(Mang^{(j)}\right)$, color $(Cor^{(j)})$and pH $(pH^{(j)})$ are parameters of the municipality j. We used two models: model 1 does not include DWC and model 2 is the final model and includes all or some DWC, as appropriate.

Non-parametric functions $\mathrm{s}_1$ and $\mathrm{s}_2$ are one- and two-dimensional smooth functions to allow for possible nonlinearities in the effect of time (year), water parameters and space (a pair of coordinates for each municipality centroid) predictors using spline functions (smoothers) [41].

A stepwise forward regression procedure was performed starting with the basic model (model 1) and adding variables one at a time to select a final best model (model 2) with some or all DWC parameters. To compare models we used the Akaike Information Criterion (AIC), which is a measure of model fit that penalizes models with too many predictors. The first DWC candidate variable to be included in the model 1 was the one with the lowest AIC amongst the set of models: model 1 with the addition of a DWC. The second inclusion was performed in the same manner, and this procedure was repeated for all the different water components until we obtained the lowest possible AIC. Parameter significance for the final model was set to the 5% level.

All statistical analyses were performed using the statistical software R version 2.14.1 (Project for Statistical Computing).

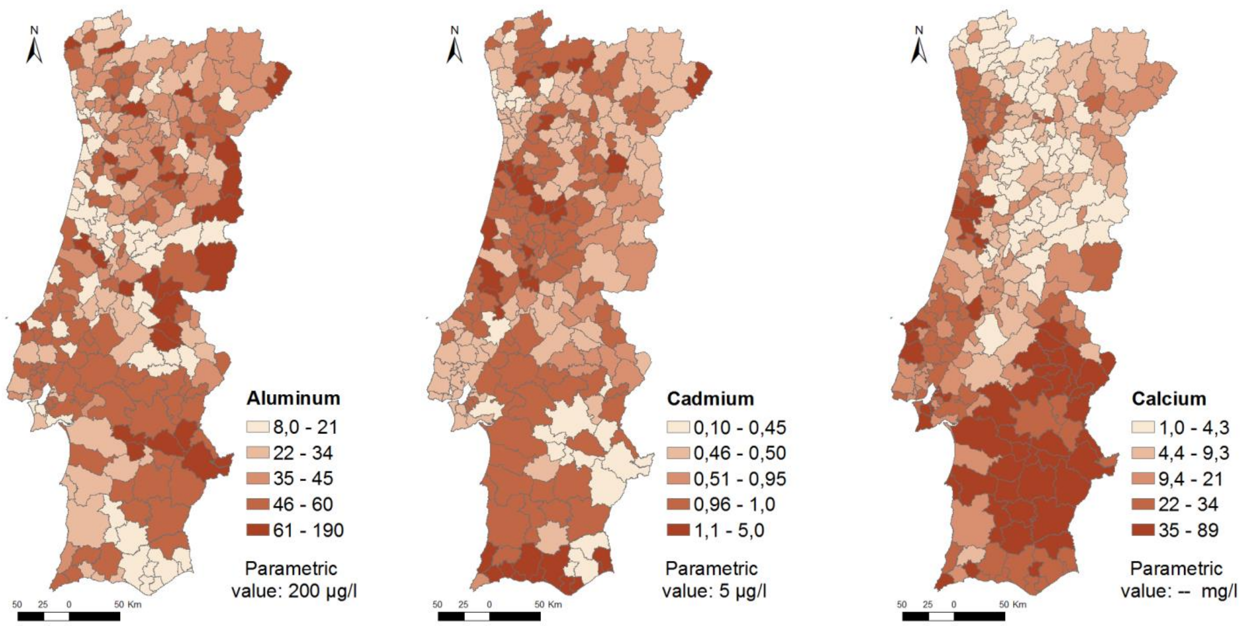
**Results**

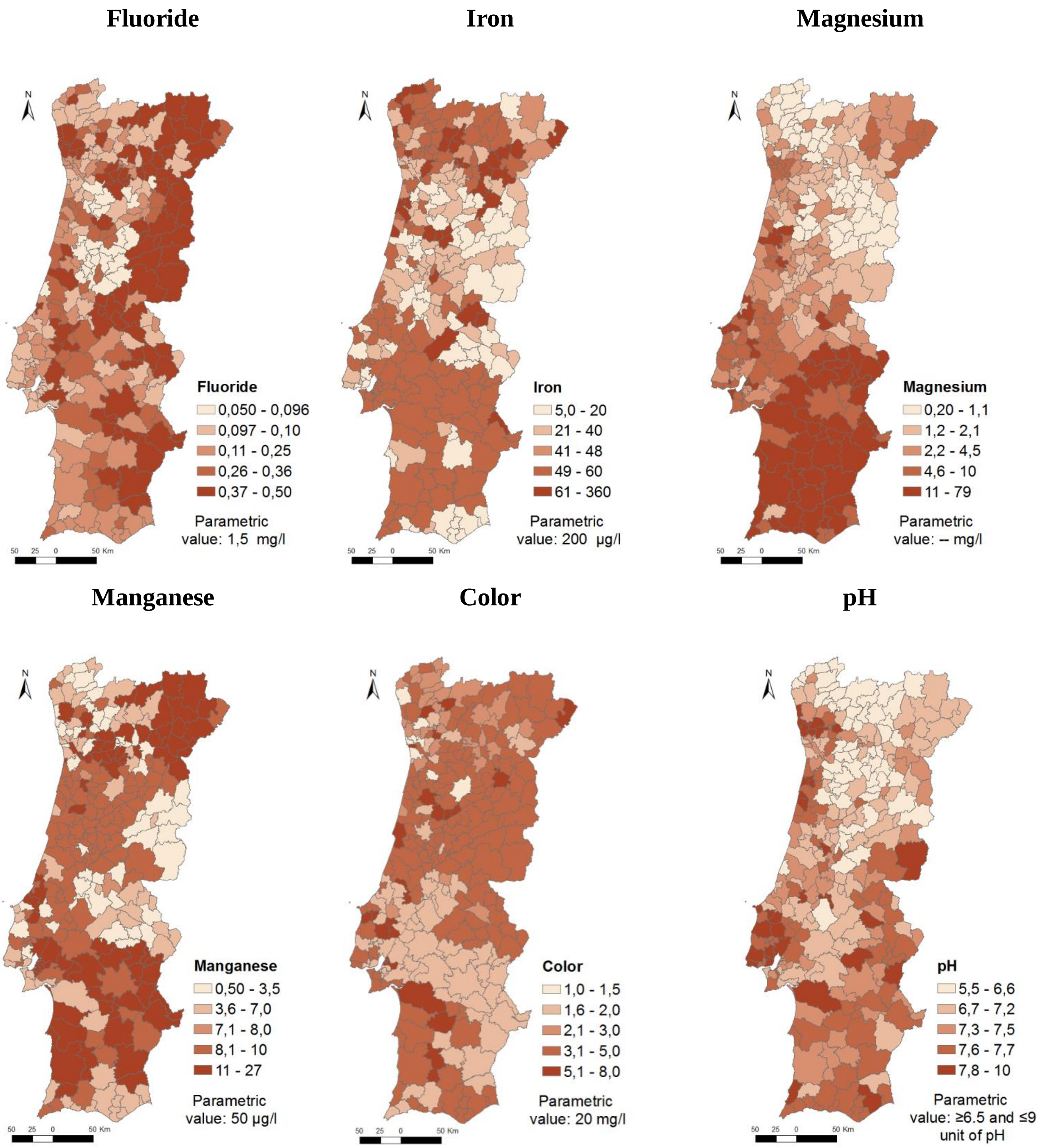
There were 97,490 hospital admissions of patients aged 50 years or over, with a diagnosis of HF during the study period. We excluded 585 registers due to missing values for the municipality of residence and, therefore, our final sample includes 96,905 (77.3% women) registers. Mean age (Standard Deviation – SD) at admission for women was 81.2 (8.5) years and for men was 78.2 (10.1) years (t-test, p-value<0.001).

Figure 2 shows the geographic distribution of each drinking water component included in the study and the correspondent regulatory parametric limits for drinking water for human consumption in Portugal [42].

**Figure 2 – Geographic distribution of mineral drinking water components in Continental Portugal (with the parametric limits of drinking water for human consumption)**

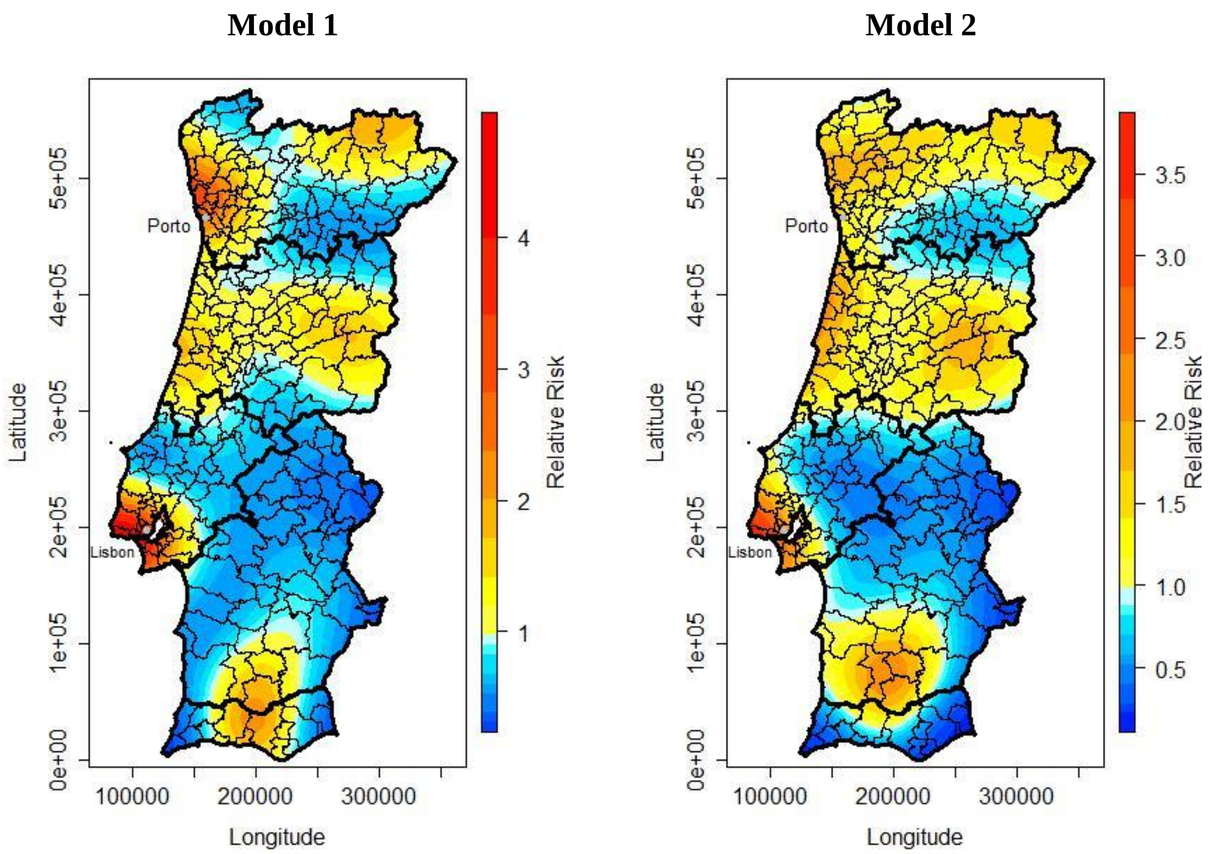
**Aluminum** **Cadmium** **Calcium**






There is a spatial effect on HF risk and we observed changes between model 1 and model 2: in model 2 the RR is lower than that in model 1 suggesting that drinking water composition might interfere in the spatial distribution of HF risk (Figure 3). It is clear the attenuated effect on HF risk in regions around Porto (northwest) and Lisbon (central west) with the inclusion of drinking water parameters in the analysis.

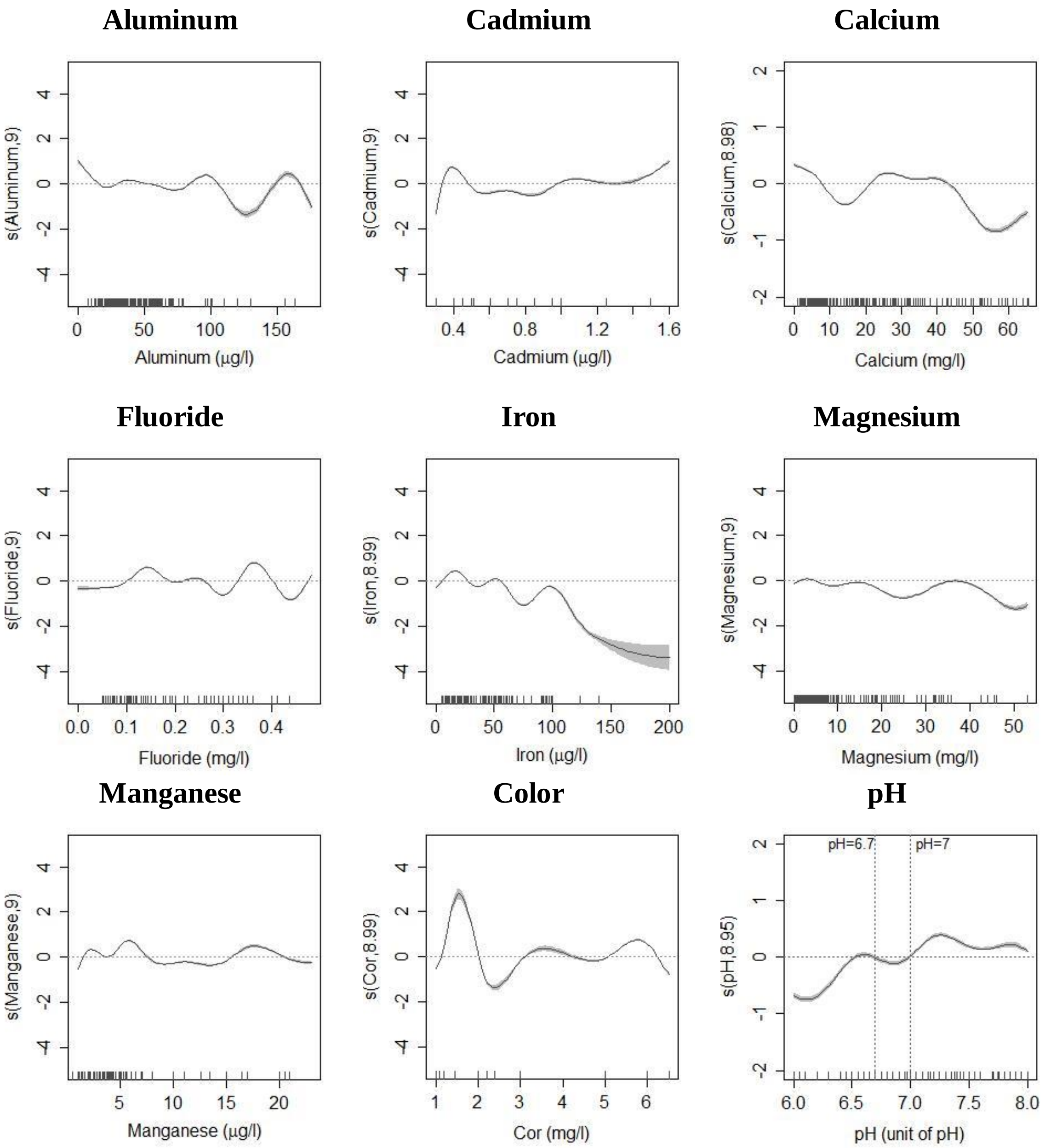
**Figure 3 – Estimated spatial effect on hip fracture risk**




**Model 1: adjusted for sex, age group, regional socioeconomic status, rural condition and temporal effects**
**Model 2: adjusted for the same covariables as in model 1 and for drinking water composition effects**

Figure 4 shows the effect of each municipality drinking water component on the risk of HF. It seems that there is no effect of aluminum, cadmium, fluoride and manganese on HF risk, neither of color; values fluctuate around the mean suggesting a non-clear or non-relation between such components and HF. However, it seems to exist a clear dose-response relationship in the concentration of iron: a reduction of the risk of HF is observed per an increase of iron concentration. Calcium and magnesium seem to have an attenuated effect on the risk of HF, as the concentration of both components increases, we observe a slight reduction of HF risk. Regarding pH, it seems that between 6.7 and 7 pH there is a lower risk than in more basic water (pH unit >7) and between 6.5-6.7 pH unit.

**Figure 4 – Estimated drinking water composition effect on hip fracture risk and 95% confidence interval**




**Model 2: adjusted for sex, age group, regional socioeconomic status, rural condition and temporal and spatial effects**

## Discussion

The association between the mineral composition of drinking water and HF has been described in previous studies, although no consensual results were found. Moreover, the effect of DWC on the spatial distribution of HF is not well described.

We found spatial differences in the risk of HF after inclusion of DWC in the model suggesting that municipality DWC might influence HF risk. This is biologically plausible since lifetime exposure to minerals in the drinking water may lead to a continuous deposition of minerals in the bones, therefore, contributing to its fragility and consequently to the increased risk of fractures. Among the water components and proprieties that we analyzed, associations with HF risk were found only for calcium, iron and magnesium and for some pH intervals.

Regarding calcium in the drinking water, we observe that an increasing concentration, until 15 mg/l, is associated with a decreasing risk of HF but after that threshold, the association is not so clear. This inverse association between calcium concentration in the drinking water and risk of fractures might be due to the positive effect of this mineral on the bone formation that is shown in some studies such as in France [43, 44] and in the USA [45]. The absorption and bioavailability of the calcium present in the drinking water is comparable, or even higher, than of the calcium present in the dairy products [46]; a study with participants from four centers in the USA, compared the effect of calcium by daily intake and by drinking water consumption – for a of 100 mg dose the protective effect on bone density of calcium in the drinking water was higher than the same amount of calcium in the diet, although such differences were not statistically significant [47]. The protective effect of calcium in the bone health, however, seem to be potentiated by the presence of vitamin D supplementation [48], while in the absence of vitamin D the protective effect of calcium seems to be inhibited [49].

We also found an inverse association between HF risk and iron concentration in the drinking water and this is compatible with descriptions in the literature, which suggests that lower levels of iron might be associated with osteoporosis [50]; iron is involved in the activation of vitamin D, affecting calcium absorption [51] and acts as a cofactors for enzymes involved in collagen important for bone formation [51, 52]. On the other hand, a high concentration of iron may act as a toxic to bone cells, therefore, contributing to osteoporosis [52, 53]. Nevertheless, it is not clear if the harmful effect of iron is due to iron itself or it is caused by another mechanism [52], as inhibits osteoblast function through higher oxidation stress [54].

Our results show a decreasing risk of HF per an increase of magnesium concentration, and this corroborates the results found in Norway [16]. It is not clear the influence of magnesium on fractures [40], although there is some evidence that magnesium has an effect on parathyroid hormone (PTH) secretion and on the calcium homeostasis that can promote the bone formation and the increase of bone strength [55]. Insufficiency of magnesium has been associated with reduced 1,25-dihydroxyvitamin D in serum and thus reduced intestinal calcium absorption [55, 56]. Also, it was suggested that magnesium might have an anti-inflammatory effect by controlling the production of RANK-L and other mechanisms of osteoclast activation that are responsible for the bone reabsorption [55, 57]. Studies indicate that low and high levels of magnesium might be harmful to bone health [40, 58-60]. In our study we did not have high values of magnesium (above the limits defined by law as safe for human health), therefore, our results reflect mainly the association with low exposure levels.

We found a lower risk of HF for pH between 6.7 and 7.0 than in more basic waters (>7 pH unit) and between 6.5-6.7. In the literature, acid waters have been associated with higher risk for HF [16] and for forearm fractures [17]. Water with low pH usually contains little hydrogen, carbonate, calcium and magnesium [17], which are important elements to maintain the bone quality. *In vitro* studies showed that acid environmental in bone cells promotes the bone resorption and the expulsion of minerals from bone cells to the exterior growth medium [61] and this was also observed *in vivo* studies with lower pH in blood being associated with an increase in urinary excretion of calcium and magnesium [27].

Our results did not confirm the associations between HF risk and concentrations of aluminum, cadmium, fluoride and manganese in the drinking water, as reported in several other countries. Associations reported in the literature are mainly showing the harmful effect of high concentrations of aluminum and cadmium in bone quality and since our samples revealed low values for these components, under the safe limits for human health, this might explain why we did not find a clear relation with HF risk. Fluoride is among the most studied components of drinking water since the 1960´s and 1970´s decades when many countries adopted the fluoridation of water, mainly to improve oral health. In Portugal, water fluoridation was not an option; there was, however, an experience fluoridation of public water supply, between 1961 and 1975 in one municipality (Montemor-o-Novo) [62]. Many studies analyzed the effect of exposure to fluoride in water and results are not consensual: there are some evidence of beneficial effects of fluoride in bone health [20, 26, 63] and a direct association with HF risk in USA [64, 65], France [66] and UK [67] while no association was found in Finland [36], Swedish [68] and USA [69]. In Finland [68], the risk of HF in a region with 1mg/L concentration of fluoride in drinking water was 50% lower than in a region without water fluoridation, however, a further follow-up study showed that when adjusted for age and sex this effect disappeared [36]. In China, higher HF risk was observed in a population exposed to fluoride concentration levels between 1.00 and 1.06 ppm [63].

Less is known about the effect of manganese on drinking water and the bone health. However, manganese is important for the synthesis of mucopolysaccharides in a bone matrix formation and is a cofactor for some enzymes in bone tissues which is essential for bone quality and growth [70]. It is shown a higher gain in bone quality with a combined between manganese and calcium supplementation in postmenopausal women when compared with calcium alone [71].

Our results should be interpreted with caution since there are some limitations, inherent to the study design and to the available data. We used national secondary data on hospital admissions that do not include registers from private hospitals, which could be seen as a limitation, although in Portugal the public hospitals treat almost the totality of HF and, therefore, the national discharge register can be seen as a nationwide portrait. The relation of DWC and HF is influenced by the slow deposition of minerals in the bones due to lifetime exposure. Therefore, using a single value for each water component, corresponding to the mean of the two medians of all samples in each municipality, in 2011 and in 2012, can be seen as an important limitation; this could be true if we were analyzing parameters of water quality, which deeply change over time. Nevertheless, we are analyzing the mineral composition of drinking water, which is mainly determined by the lithological and geological characteristics [29, 72] of the water source place and we do not expect important changes over time at municipality scale. Moreover, this is an ecological study and we are not evaluating individual exposure to DWC.

The major strengths of our study include the large-scale population-based design that allows a high statistical power able to detect small relative differences in HF and the data from nationwide registers that minimize the risk of selection and information bias. There are accentuated inequalities in the risk of HF in Portugal, and we could partially explain such geographic patterns by differences in the exposure to minerals present in drinking water.

## Conclusions

We found a significantly reduced risk of HF associated with higher concentration (within the regulatory limits for human consumption) of calcium, magnesium, and iron in the drinking water. We did not find a relation between aluminum, cadmium, fluoride and manganese concentration in the drinking water, or water color and the HF risk. Our study seems to indicate the risk of HF is lower for neutral drinking water. This study gives some important insights about the influence of drinking water in the risk of HF, but other studies are needed in order to clarify the associations found here. A better knowledge of the association between environmental factors and HF incidence can help to better health policy decisions in the prevention of HF and contribute to a healthy aging.

## References

1. Aaseth J, Boivin G, Andersen O. Osteoporosis and trace elements--an overview. J Trace Elem Med Biol. 2012;26(2-3):149-52. Epub 2012/05/12.

2. Alfven T, Elinder CG, Hellstrom L, Lagarde F, Jarup L. Cadmium exposure and distal forearm fractures. J Bone Miner Res. 2004;19(6):900-5. Epub 2004/05/06.

3. Burge R, Dawson-Hughes B, Solomon DH, Wong JB, King A, Tosteson A. Incidence and economic burden of osteoporosis-related fractures in the United States, 2005-2025. Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research. 2007;22(3):465-75. Epub 2006/12/06.

4. Ballane G, Cauley JA, Luckey MM, Fuleihan Gel H. Secular trends in hip fractures worldwide: opposing trends East versus West. Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research. 2014;29(8):1745-55. Epub 2014/03/20.

5. Litwic A, Edwards M, Cooper C, Dennison E. Geographic differences in fractures among women. Womens Health (Lond Engl). 2012;8(6):673-84. Epub 2012/11/28.

6. Cheng SY, Levy AR, Lefaivre KA, Guy P, Kuramoto L, Sobolev B. Geographic trends in incidence of hip fractures: a comprehensive literature review. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA. 2011;22(10):2575-86. Epub 2011/04/13.

7. IOF I. HIP FRACTURE INCIDENCE MAP. 2015; Available from: http://www.iofbonehealth.org/facts-and-statistics/hip-fracture-incidence-map.

8. de Pina MF, Alves SM, Barbosa M, Barros H. Hip fractures cluster in space: an epidemiological analysis in Portugal. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA. 2008;19(12):1797-804. Epub 2008/06/10.

9. Prentice A. Diet, nutrition and the prevention of osteoporosis. Public health nutrition. 2004;7(1A):227-43. Epub 2004/02/20.

10. Kannus P. Preventing osteoporosis, falls, and fractures among elderly people. Promotion of lifelong physical activity is essential. BMJ. 1999;318(7178):205-6. Epub 1999/01/23.

11. Oliveira CM, Economou T, Bailey T, Mendonca D, Pina MF. The interactions between municipal socioeconomic status and age on hip fracture risk. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA. 2015;26(2):489-98. Epub 2014/10/26.

12. CHSR. Human Health Effects of Heavy Metals. Center for Hazardous Substance Research - Environmental Science and Technology Briefs for Citizens, 2009.

13. WHO. Nutrients in Drinking Water Geneva World Health Organization, 2005.

14. Simonen O, Laitinen O. Does fluoridation of drinking-water prevent bone fragility and osteoporosis? Lancet. 1985;2(8452):432-4. Epub 1985/08/24.

15. Rylander R. Drinking water constituents and disease. The Journal of nutrition. 2008;138(2):423S-5S. Epub 2008/01/22.

16. Dahl C, Sogaard AJ, Tell GS, Flaten TP, Hongve D, Omsland TK, et al. Nationwide data on municipal drinking water and hip fracture: could calcium and magnesium be protective? A NOREPOS study. Bone. 2013;57(1):84-91. Epub 2013/07/09.

17. Dahl C, Sogaard AJ, Tell GS, Flaten TP, Krogh T, Aamodt G. Is the quality of drinking water a risk factor for self-reported forearm fractures? Cohort of Norway. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA. 2013;24(2):541-51. Epub 2012/05/10.

18. Nieves JW. Osteoporosis: the role of micronutrients. The American journal of clinical nutrition. 2005;81(5):1232S-9S. Epub 2005/05/11.

19. Chapuy MC, Arlot ME, Duboeuf F, Brun J, Crouzet B, Arnaud S, et al. Vitamin D3 and calcium to prevent hip fractures in the elderly women. The New England journal of medicine. 1992;327(23):1637-42. Epub 1992/12/03.

20. Aaseth J, Boivin G, Andersen O. Osteoporosis and trace elements--an overview. J Trace Elem Med Biol. 2012;26(2-3):149-52. Epub 2012/05/12.

21. Smoliar VI. [Effect of iron-deficient diets on the formation of bone tissue]. Voprosy pitaniia. 1984(5):55-9. Epub 1984/09/01. Vliianie ratsionov s defitsitom zheleza na formirovanie kostnoi tkani.

22. Sojka JE, Weaver CM. Magnesium supplementation and osteoporosis. Nutrition reviews. 1995;53(3):71-4. Epub 1995/03/01.

23. Stern PH. Biphasic effects of manganese on hormone-stimulated bone resorption. Endocrinology. 1985;117(5):2044-9. Epub 1985/11/01.

24. Monteagudo FS, Cassidy MJ, Folb PI. Recent developments in aluminum toxicology. Medical toxicology and adverse drug experience. 1989;4(1):1-16. Epub 1989/01/01.

25. Staessen JA, Roels HA, Emelianov D, Kuznetsova T, Thijs L, Vangronsveld J, et al. Environmental exposure to cadmium, forearm bone density, and risk of fractures: prospective population study. Public Health and Environmental Exposure to Cadmium (PheeCad) Study Group. Lancet. 1999;353(9159):1140-4. Epub 1999/04/21.

26. Vestergaard P, Jorgensen NR, Schwarz P, Mosekilde L. Effects of treatment with fluoride on bone mineral density and fracture risk--a meta-analysis. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA. 2008;19(3):257-68. Epub 2007/08/19.

27. Frings-Meuthen P, Baecker N, Heer M. Low-grade metabolic acidosis may be the cause of sodium chloride-induced exaggerated bone resorption. Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research. 2008;23(4):517-24. Epub 2007/12/07.

28. Vormann J. Magnesium: nutrition and metabolism. Molecular aspects of medicine. 2003;24(1-3):27-37. Epub 2003/01/23.

29. Cortez J. Águas Minerais Naturais e de Nascente da Região Centro. Liberum M, editor. Aveiro2012. 526 p.

30. Population Ageing in the United Kingdom, its Constituent Countries and the European Union. http://www.ons.gov.uk/ons/dcp171776_258607.pdf2012 [cited 2014 14-12-2104].

31. INE. *Instituto Nacional de Estatística*; [cited 2012]; Available from: www.ine.pt.

32. ERSAR. CONHEÇA OS SERVIÇOS DE ÁGUAS E RESÍDUOS EM PORTUGAL. 2013.

33. INAG. Tipologia de rios em portugal continental no âmbito da implementação da directiva quadro da água. Lisboa2008.

34. ERSAR. Relatório anual dos serviços de água e resíduos em Portugal: Lisboa; 2012.

35. Alves SM, Castiglione D, Oliveira CM, de Sousa B, Pina MF. Age-period-cohort effects in the incidence of hip fractures: political and economic events are coincident with changes in risk. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA. 2014;25(2):711-20. Epub 2013/08/29.

36. Alhava EM, Olkkonen H, Kauranen P, Kari T. The effect of drinking water fluoridation on the fluoride content, strength and mineral density of human bone. Acta orthopaedica Scandinavica. 1980;51(3):413-20. Epub 1980/06/01.

37. Alloway BJ, editor. Heavy Metals in Soils: Trace Metals and Metalloids in Soils and their Bioavailability: Springer Netherlands; 19201394.

38. Bellof G, Most E, Pallauf J. Concentration of copper, iron, manganese and zinc in muscle, fat and bone tissue of lambs of the breed German Merino Landsheep in the course of the growing period and different feeding intensities. Journal of animal physiology and animal nutrition. 2007;91(3-4):100-8. Epub 2007/03/16.

39. Budis H, Kalisinska E, Lanocha N, Kosik-Bogacka DI. The concentration of manganese, iron and strontium in bone of red fox Vulpes vulpes (L. 1758). Biological trace element research. 2013;155(3):361-9. Epub 2013/09/10.

40. Castiglioni S, Cazzaniga A, Albisetti W, Maier JA. Magnesium and osteoporosis: current state of knowledge and future research directions. Nutrients. 2013;5(8):3022-33. Epub 2013/08/06.

41. Wood SN. Generalized Additive Models: An Introduction with R. . Press CaHC, editor2006.

42. Diário da República, 1.ª série — N.º 164 — 27 de Agosto de 2007, (2007).

43. Aptel I, Cance-Rouzaud A, Grandjean H. Association between calcium ingested from drinking water and femoral bone density in elderly women: evidence from the EPIDOS cohort. Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research. 1999;14(5):829-33. Epub 1999/05/13.

44. Guillemant J, Le HT, Accarie C, du Montcel ST, Delabroise AM, Arnaud MJ, et al. Mineral water as a source of dietary calcium: acute effects on parathyroid function and bone resorption in young men. The American journal of clinical nutrition. 2000;71(4):999-1002. Epub 2000/03/25.

45. Meunier PJ, Jenvrin C, Munoz F, de la Gueronniere V, Garnero P, Menz M. Consumption of a high calcium mineral water lowers biochemical indices of bone remodeling in postmenopausal women with low calcium intake. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA. 2005;16(10):1203-9. Epub 2005/03/04.

46. Bohmer H, Muller H, Resch KL. Calcium supplementation with calcium-rich mineral waters: a systematic review and meta-analysis of its bioavailability. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA. 2000;11(11):938-43. Epub 2001/02/24.

47. Bauer DC, Browner WS, Cauley JA, Orwoll ES, Scott JC, Black DM, et al. Factors associated with appendicular bone mass in older women. The Study of Osteoporotic Fractures Research Group. Annals of internal medicine. 1993;118(9):657-65. Epub 1993/05/01.

48. Reid IR, Bolland MJ, Grey A. Effect of calcium supplementation on hip fractures. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA. 2008;19(8):1119-23. Epub 2008/02/21.

49. DIPART VDIPAoRTG. Patient level pooled analysis of 68 500 patients from seven major vitamin D fracture trials in US and Europe. BMJ. 2010;340:b5463. Epub 2010/01/14.

50. D'Amelio P, Cristofaro MA, Tamone C, Morra E, Di Bella S, Isaia G, et al. Role of iron metabolism and oxidative damage in postmenopausal bone loss. Bone. 2008;43(6):1010-5. Epub 2008/09/06.

51. Palacios C. The role of nutrients in bone health, from A to Z. Critical reviews in food science and nutrition. 2006;46(8):621-8. Epub 2006/11/10.

52. Ilich JZ, Kerstetter JE. Nutrition in bone health revisited: a story beyond calcium. Journal of the American College of Nutrition. 2000;19(6):715-37. Epub 2001/02/24.

53. Weinberg ED. Iron loading: a risk factor for osteoporosis. Biometals : an international journal on the role of metal ions in biology, biochemistry, and medicine. 2006;19(6):633-5. Epub 2006/05/02.

54. He YF, Ma Y, Gao C, Zhao GY, Zhang LL, Li GF, et al. Iron overload inhibits osteoblast biological activity through oxidative stress. Biological trace element research. 2013;152(2):292-6. Epub 2013/01/22.

55. Rude RK, Singer FR, Gruber HE. Skeletal and hormonal effects of magnesium deficiency. Journal of the American College of Nutrition. 2009;28(2):131-41. Epub 2009/10/16.

56. Fatemi S, Ryzen E, Flores J, Endres DB, Rude RK. Effect of experimental human magnesium depletion on parathyroid hormone secretion and 1,25-dihydroxyvitamin D metabolism. The Journal of clinical endocrinology and metabolism. 1991;73(5):1067-72. Epub 1991/11/01.

57. Malpuech-Brugere C, Nowacki W, Daveau M, Gueux E, Linard C, Rock E, et al. Inflammatory response following acute magnesium deficiency in the rat. Biochimica et biophysica acta. 2000;1501(2-3):91-8. Epub 2000/06/06.

58. Michaelsson K, Holmberg L, Mallmin H, Sorensen S, Wolk A, Bergstrom R, et al. Diet and hip fracture risk: a case-control study. Study Group of the Multiple Risk Survey on Swedish Women for Eating Assessment. International journal of epidemiology. 1995;24(4):771-82. Epub 1995/08/01.

59. New SA, Bolton-Smith C, Grubb DA, Reid DM. Nutritional influences on bone mineral density: a cross-sectional study in premenopausal women. The American journal of clinical nutrition. 1997;65(6):1831-9. Epub 1997/06/01.

60. Ryder KM, Shorr RI, Bush AJ, Kritchevsky SB, Harris T, Stone K, et al. Magnesium intake from food and supplements is associated with bone mineral density in healthy older white subjects. Journal of the American Geriatrics Society. 2005;53(11):1875-80. Epub 2005/11/09.

61. Wynn E, Krieg MA, Aeschlimann JM, Burckhardt P. Alkaline mineral water lowers bone resorption even in calcium sufficiency: alkaline mineral water and bone metabolism. Bone. 2009;44(1):120-4. Epub 2008/10/18.

62. Duarte ME. Os Fluoretos na água de consumo humano 2008.

63. Li Y, Liang C, Slemenda CW, Ji R, Sun S, Cao J, et al. Effect of long-term exposure to fluoride in drinking water on risks of bone fractures. Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research. 2001;16(5):932-9. Epub 2001/05/09.

64. Jacobsen SJ, Goldberg J, Miles TP, Brody JA, Stiers W, Rimm AA. Regional variation in the incidence of hip fracture. US white women aged 65 years and older. Jama. 1990;264(4):500-2. Epub 1990/07/25.

65. Danielson C, Lyon JL, Egger M, Goodenough GK. Hip fractures and fluoridation in Utah's elderly population. Jama. 1992;268(6):746-8. Epub 1992/08/12.

66. Cauley JA, Murphy PA, Riley TJ, Buhari AM. Effects of fluoridated drinking water on bone mass and fractures: the study of osteoporotic fractures. Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research. 1995;10(7):1076-86. Epub 1995/07/01.

67. Cooper C, Wickham CA, Barker DJ, Jacobsen SJ. Water fluoridation and hip fracture. Jama. 1991;266(4):513-4. Epub 1991/07/24.

68. Alffram PA, Hernborg J, Nilsson BE. The influence of a high fluoride content in the drinking water on the bone mineral mass in man. Acta orthopaedica Scandinavica. 1969;40(2):137-42. Epub 1969/01/01.

69. Madans J, Kleinman JC, Cornoni-Huntley J. The relationship between hip fracture and water fluoridation: an analysis of national data. American journal of public health. 1983;73(3):296-8. Epub 1983/03/01.

70. Clegg MS, Donovan SM, Monaco MH, Baly DL, Ensunsa JL, Keen CL. The influence of manganese deficiency on serum IGF-1 and IGF binding proteins in the male rat. Proc Soc Exp Biol Med. 1998;219(1):41-7. Epub 1998/09/29.

71. Strause L, Saltman P, Smith KT, Bracker M, Andon MB. Spinal bone loss in postmenopausal women supplemented with calcium and trace minerals. The Journal of nutrition. 1994;124(7):1060-4. Epub 1994/07/01.

72. Eggenkamp HGM, Marques JM. A comparison of mineral water classification techniques: Occurrence and distribution of different water types in Portugal (including Madeira and the Azores). Journal of Geochemical Exploration. 2013;132:125–39.

## 3.6 Trends in the Hip Arthroplasties: A Population-Based Study in sixteen Countries (1997-2010) from Europe, North and South of America and Oceania.

# TRENDS IN HIP ARTHROPLASTIES:

# A POPULATION-BASED STUDY IN SIXTEEN COUNTRIES (1997-2010) FROM EUROPE, NORTH AND SOUTH AMERICA, AND OCEANIA

**Oliveira CM, Pina MF**

**Carla Oliveira**

i3S - Instituto de Investigação e Inovação em Saúde, Universidade do Porto, Portugal;

INEB - Instituto de Engenharia Biomédica, Universidade do Porto, Rua do Campo Alegre, 823, 4150-180 Porto, Portugal;

ESTSP/IPP - Escola Superior de Tecnologia da Saúde do Porto, Instituto Politécnico do Porto, Rua Valente Perfeito, 322, 4400-330 Vila Nova de Gaia, Portugal;

Departamento de Epidemiologia Clínica, Medicina Preditiva e Saúde Pública,

FMUP - Faculdade de Medicina da Universidade do Porto, Al. Prof. Hernâni Monteiro, 4200 - 319 Porto, Portugal

ISPUP - Instituto de Saúde Pública da Universidade do Porto, Rua das Taipas 135, 4050-600, Porto, Portugal

carlaoliveir@ineb.up.pt

**Maria Fátima Pina**

ICICT/FIOCRUZ - Instituto de Comunicação e Informação em Saúde/Fundação Oswaldo Cruz, Av. Brasil 4365, Av. Brasil, 4.365 - Pavilhão Haity Moussatché - Manguinhos, Rio de Janeiro, CEP: 21040-900,

i3S - Instituto de Investigação e Inovação em Saúde, Universidade do Porto, Portugal;

INEB - Instituto de Engenharia Biomédica, Universidade do Porto, Rua do Campo Alegre, 823, 4150-180 Porto, Portugal;

FMUP - Faculdade de Medicina da Universidade do Porto, Al. Prof. Hernâni Monteiro, 4200 - 319 Porto, Portugal

fatima.pina@icict.fiocruz.br

**Corresponding author**: C M Oliveira; coliveir@ineb.up.pt; phone: +351 226074900 ; Fax: +351 226094567; INEB, Instituto de Engenharia Biomédica, Universidade do Porto, Rua do Campo Alegre, 823, 4150-180 Porto, Portugal

**Acknowledgments**: The work was financed by Portuguese funds through FCT – Fundação para a Ciência e a Tecnologia in the framework of project UID/BIM/04293/2013. Authors would also like to thank FCT for the grant PTDC/SAU-EPI/113424/2009.

**Disclosure Statement**: Carla Maria Oliveira and Maria Fátima Pina declare that they have no conflict of interest.

**Role of funding source**: The funder Fundação para a Ciência e Tecnologia - FCT has no role in this paper.

## ABSTRACT

**Background:** Increasing aging population and improving medical care lead to an expected increase of total hip arthroplasties (THA) to satisfy the requirement. However, economic, social and political changes that have been seen in some countries, may result in some changes in what is expected.

**Objectives:** To explore temporal trends (1997-2010) of THA incidence rates for sixteen countries (1997-2010) from Europe, North and South America, and Oceania, providing projections between 2010 and 2015.

**Methods:** Different sources provided the national number of THAs, which was available in sixteen countries from Europe, North and South of America and Oceania. Data was aggregated by year (14 years, 1997-2010), by four age groups (45-64; 65-74; 75-84; >84), and by sex. Generalized Additive Models (GAM) was used assuming that the number of THA follows a Poisson distribution to identify shape and points where the trend changes significantly in magnitude and direction and to quantify changes in the estimated and projected crude incidence rates (CIRs), age-standardized incidence rates (ASIRs) and standard morbidity rates (SMRs). The standardization was performed using the indirect method of standardization and the USA population in 1997 as a reference.

**Results:** Results shows a generally increase in trend in the overall period (if the constant growth rate is assumed). However, this increase is not linear and different pattern was observed: England and Wales for both sexes and in Finland, France, and Italy for men and in New Zealand for women showed a pattern of increase followed by stabilization; Switzerland, Spain and Portugal for both sexes and Italy for women showed a pattern of increase followed by decrease; France showed a pattern of decrease; and in Brazil, even while having an overall pattern of growth (if constant growth rate is assumed), a period of instability was observed around 2005, a peak of increase followed by decrease was detected.

**Conclusions:** Higher variability between countries in THA incidence rates was found. An increasing trend in almost every country since 1997 in almost countries was

observed with an alarming decrease in countries with some economic constraints, which has led us to consider that this may not be a reduction based on people's needs, but rather an issue of cost reduction.

**Keywords:** total hip arthroplasties, epidemiology, temporal trend, countries variability

## Introduction

Total hip arthroplasty (THA) is the most common surgical procedure to treat patients with osteoarthritis, rheumatoid arthritis, and avascular necrosis when conventional medical therapy fails [1, 2]. Hip fracture is another condition that leads, in almost every case, to THA [3]. This procedure is effective and considered one of the most successful medical interventions for long-term survival [4], as well as the most cost-effective surgical procedure [5-7] in patients with such conditions, which improves their quality of life, increases mobility, reduces pain and maintains their independence [8].

THA is most frequently performed on individuals between 65 and 79 years of age, however being older or younger is not a contraindication for surgery. THA is performed on women more often than on men [2, 9] and the trend pattern is similar in both sexes [9]. In the youngest and oldest, the age-specific incidence rates are low and similar for both sexes, although this seems to have changed most recently (from 2000 to 2010) and the number of operations has increased significantly in those 55 to 64 and above 80 years of age [9].

Relatively little work has been published regarding the comparison between countries in THA and the work that has been done has only been published in country-specific journals and languages in many cases [10]. However, in the few studies found, a higher variability was found between countries [11]. There are countries where these registries didn’t even exist for comparison [10]. In Europe, the Scandinavian countries contribute to stimulating development of these registries; first in Sweden in 1979 [10], then in Norway in 1987 [10], followed by Finland in 1993 [10], Denmark in 1995 [10], Germany in 1997 [10], Australia and New Zealand in 1999 [10], Canada in 2001 [10], England, Wales and Slovakia in 2003 [10] and Switzerland in 2004 [10]. A study showing the differences and opportunities of primary THA in different countries from Europe, Asia, Oceania and North America in 1998 shows that European countries had the highest incidence of THA, with the most cases in France with 135 per 100,000 person-year; followed by Norway, Sweden, Finland with 121, 118 and 93 per 100,000 person-year, respectively; and then in Denmark, Iceland and Scotland where the incidence varied between 90 and 81 per 100,000 person-year [12]. The incidence in Australia (73 per 100,000 person-year) is lower than some of the countries of Central

Europe; however, there are some exceptions, such as England, Wales, Hungary and Ireland, which vary between 71 and 63 per 100,000 person-year. The incidence in the USA (53 per 100,000 person-year) is lower than in Australia and in some Southern European countries; like Portugal, Spain, and Italy [12]. Asian countries, such as Singapore, had a significantly lower incidence of THA than European countries, Australia and the United States (USA) with only 8 per 100,000 person-year [12]. These differences can be due to differences in surgical procedures and recommendations, in the choice of an appropriate implant, and in the criterion for patient selection that can be similar between developed healthcare systems; however, in less developed areas, such as Eastern Europe, many Asian countries, and Central and South America, the reality can be quite different [12].

Many studies have been reporting an increasing (rates) treatment with THA, especially due to proven benefit. An increased rate of THA was shown at 16% (1991-2004) in patients aged 45 years and older [8] in the United Kingdom, 18% (between 1991 and 2000) in patients aged 35 years and older [9] and 29% (1990-1995) in England [12], 46% (1990-2002) [13] in the USA, 20% (1990-1998) in Australia, 29% (1985-1998) in Denmark, 111% (1985-1998) in Finland, 37% (1995-1999) in Hungary, 45% (1985-1999) in Iceland, 27% (1985-1998) in Norway, 72% (1990-1998) in Scotland, 33% (1995-1998) in Singapore, 16% (1990-1995) in Sweden, 4% (1995-1998) in the United States [12]; but a reduction of 12% (1995-1998) in Ireland, 4% (1985-1990) in Sweden, 12% (1995-1998) in Wales [12], and 20% in Australia (1994-1998) [14]. Other studies did not even quantify or visually show an increase, such as in the USA [15]. Others, instead of using rates, quantified the increase in terms of absolute number, and an increase of 20% (1986) was observed in Sweden [16], 68% (1986-1997) in the Netherlands [16] and 25.9% (1994-1998) [14] in the U.K. Most of the countries show an increase in temporal trends, and with the increase of aging populations and improved medical care, especially in developing countries, the incidence of THA is expected to continually increase to satisfy needs [7]. However, economic, social and political changes that have recently been seen in some countries, especially in European countries, may have some impact on these recent tendencies.

The aim of this study is to examine the temporal trends of THAs incidence rates, from 1997 to 2010, in individuals over 45 years of age, in different countries from Europe, North and South America, and Oceania providing projections between 2010 and 2015.

**Material and Methods**

**Data**

Different sources provided the number of THAs, which was available in sixteen countries: Nationwide Inpatient Sample provided data for the United States of America (USA); Hospital Morbidity Database for Canada; Registro de Altas – CMB for Spain; National Hospital Discharge Register (NHDR) for Portugal, Netherlands, Finland Australia and Germany; National Hospital Database for France; Hospital Discharge Records Database for Italy; Hospital Statistical FSO for Switzerland; Database SUS (Sistema Único de Saúde) for Brazil; annual reports of each country for Denmark, England and Wales, New Zealand and Slovakia.

When possible, data was aggregated by year (14 years, 1997-2010), by four age groups, and by sex. The four age groups were 45-64; 65-74; 75-84; >84 and when this aggregation was not possible (e.g. Denmark), the age group used was: 40-59; 60-69; 70-79; >79. The desired data aggregation was not possible to obtain directly from the resources in all cases; therefore, in these instances, the number of THA was estimated proportionally following two types of situations: (1) the total cases were possible to obtain stratified by year and age group and by year and sex (Slovakia); (2) the total cases were possible to obtain stratified by year, by sex and by age group (New Zealand); the estimation was performed proportionally for each case to obtain the total cases stratified by year, sex, and age group. There were two potential countries to include in the analysis, Sweden, and Norway, which were excluded due to the impossibility of performing this estimation. From the included countries, the number of THA was not available for all years in the period of interest. Data was available for Australia: 2003-2008 (6 years); Brazil: 2000-2010; Canada: 1997-2006 (10); Switzerland: 1998-2010 (13); Germany: 2005-2008 (4); Denmark: 2005-2010 (6); England and Wales: 2005-2010 (6); Spain: 1997-2008 (12); Finland: 1997-2010 (14); France: 2002-2007 (6);

Italy: 1999-2010 (12); Netherlands: 1997-2007 (11); New Zealand: 1999-2010 (12); Portugal: 1997-2010 (14); Slovakia: 2003-2008 (6); the USA: 1997-2010 (14).

To calculate the population at-risk or person-years, we used the year-specific population characteristics published by EUROSTAT or by the official National Institute of Statistics aggregated by country, year (1997–2010), sex, and four age groups. The age group used was the same as the age group used to aggregate THA for each country.

Considering that $NTha_{ijts}$ represents the number of THA in a specific age group $i$ ($i = 1, \ldots, 4$), in country $j$ ($j = 1, \ldots, 16$), in year ($t = 1, \ldots, 14$) and in sex $s$ ($s = 1,2$), and $NPop_{ijts}$ represents the number of population at risk in age group $i$, in country $j$, in year $t$ and in sex $s$. The Crude Incidence Rates (CIRs) were estimated and to controlled for differences that may occur due to demographic change in the population age-structure per country, the age-standardized incidence rates (ASIRs) were estimated using the indirect method of standardization, taking as reference the USA age structure population in 1997, due to the fact that this country had more literature on this topic and the annual data between 1997 and 2010 was complete. The reference rate for 1997 in the USA by age was given by the following expression:

$$r_{i\ USA\ 1997} \sim \frac{\sum_{s=1}^{2} NTha_{i\ USA\ 1997\ s}}{\sum_{s=1}^{2} NPop_{i\ USA\ 1997\ s}}$$

The expected number of THA in age group $i$, in country $j$, in year $t$ and in sex $s$ is represented by the expression $e_{ijts} = r_{i\ USA\ 1997} \times NPop_{ijts}$. Therefore, the number of THA in country $j$, in year $t$ and in sex $s$ assuming constant risk for age is given by $e_{jts} = \sum_{i=1}^{4} e_{ijts}$, i.e. the number of expected values in each country, in each year and in each sex.

### Statistical analysis

We conducted a temporal analysis for each country and sex with General Additive Models (GAM) to identify shape and points where the trend changes significantly in magnitude and direction between 1997 and 2010 and to project values (2010-2015). Annual absolute and relative changes were quantified between each turning point and within projection period using estimated values on the original scale. These models allow great flexibility as they can incorporate non-parametric functions, such as spline functions (smoothers), taking into account the possible non-linearity relationship between explanatory and response variables.

We assumed that the response variable, the number of THA, $NTha_t$, in each year $t$ is distributed as a Poisson random variable (or is distributed as a negative binomial random variable with $\theta$ scale parameter to model the overdispersion when a preliminary test reveals overdispersion in the count data) with mean $\lambda_t = e_t \rho_t$ where $e_t$ is the number of THA expected if the risk is constant and $\rho_t$ is the relative risk (RR).

For each sex and country, the models implemented to estimate the parameters of interest were:

$NTha_t \sim Pois(\lambda_t)$ or $NTha_t \sim NegBin(\lambda_t, \theta)$

$log(\lambda_t) = log(e_t \rho_t) = log(e_t) + log(\rho_t) = log(e_t) + \beta_0 + s\left(Year^{(t)}\right)$

Where $Year^{(t)}$ represent a continuous variable that varies between 1997 and 2010 and s(.) represent a smooth function to take into account possible non-linearity. The population effects were considered by including the expected number of cases $\mathrm{e_t}$ as an offset (i.e. for each sex and country, the sum of the product of the population at a given year and age group by the CIR in 1997 USA of the correspondent age group).

For each sex and country, the models can then be reorganized such that the relative risk $\rho_t$ corresponds to the standardized morbidity ratio (SMR), where $SMR = \lambda_t / \mathrm{e_t}$, i.e. the ratio of the estimated number of cases by the expected cases at a given time. These models were used to interpolate and extrapolate the SMR, the CIR and the ASIR between 1997 and 2015, being $CIR = \lambda_t / NPop_t$ and $\mathrm{ASIR} = \rho_t * r_{USA\ 1997}$ where $NPop_t$ is the number of population at risk in year $t$ and $r_{USA\ 1997}$ is the CIR for reference population (USA population in 1997):

$$r_{USA\ 1997} \sim \frac{\sum_{i=1}^{4} \sum_{s=1}^{2} NTha_{\ i\ USA\ 1997\ s}}{\sum_{i=1}^{4} \sum_{s=1}^{2} NPop_{\ i\ USA\ 1997\ s}}$$

Projection of population from 2011 to 2015 when available data was not possible to obtain from official sources an estimate was performed by GAM.

All the analyses were performed with the Statistical software R version 2.14.1 (Project for Statistical Computing) using the mgcv and MASS package.

**Results**

Figure 1 and 2 represent the estimated (1997–2010) and the projected (2010-2015) CIR and ASIR of THA (1997–2015) if each country were to have the same age structures as the USA population in 1997, as well as raw data of incidence rates represented as a *"black point"* in the figure. In terms of temporal pattern, we find a similar trend pattern between men and women in almost all cases. The overall trend increases between 1997 and 2010 in almost all countries (if constant growth rate is assumed) with the growth velocity being higher in men than in women, except in countries like Australia, Brazil, Switzerland, Germany, England and Wales, Portugal, Slovakia and the USA; and in France, where an overall trend of reduction was observed (if constant decline rate is assumed), the decline velocity being higher in women than in men.

However, the velocity of change is not constant and some turning points or change in velocity was observed in some countries during this period: a pattern of increase and posterior stabilization was observed in England and Wales for both sexes, in Finland and Italy for men, and in New Zealand for women; and a pattern of increase followed by decrease was observed in Switzerland, Spain and Portugal for both sexes and in Italy and the Netherlands for women. In France, a significant pattern of decrease was observed for women and stabilization for men. In Brazil, even while having an overall pattern of growth since 1997, a period of instability in the pattern was observed around 2005: a peak of increase followed by a decrease in both sexes (Figure 1 and 2).

**Figure 1 - Estimated and projected temporal trend (95% confidence interval) in crude and age-standardized incidence rates in women by country between 1997 and 2015**

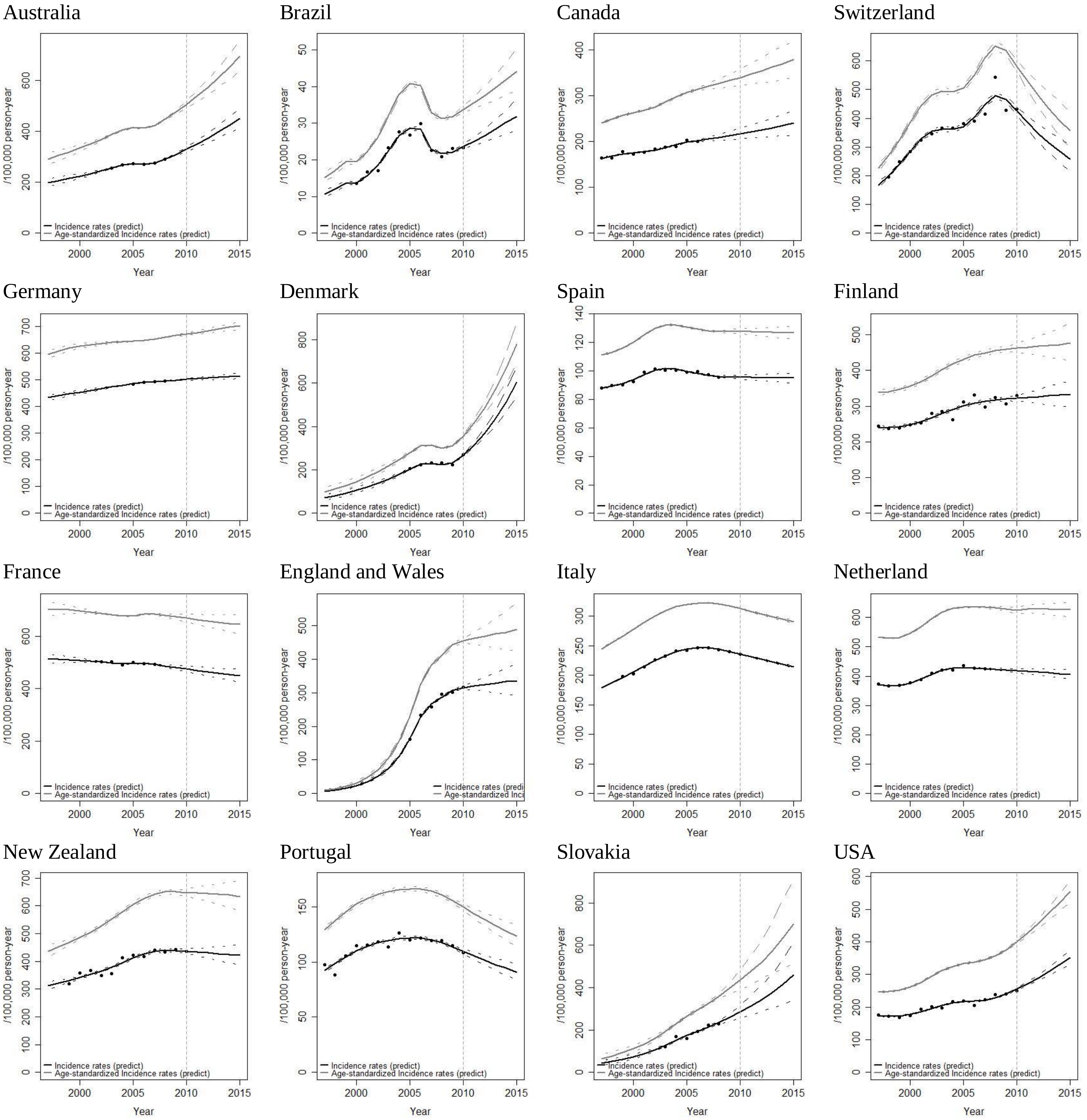


**Figure 2 – Estimated and projected temporal trend (95% confidence interval) in crude and age-standardized incidence rates in men by country between 1997 and 2015**

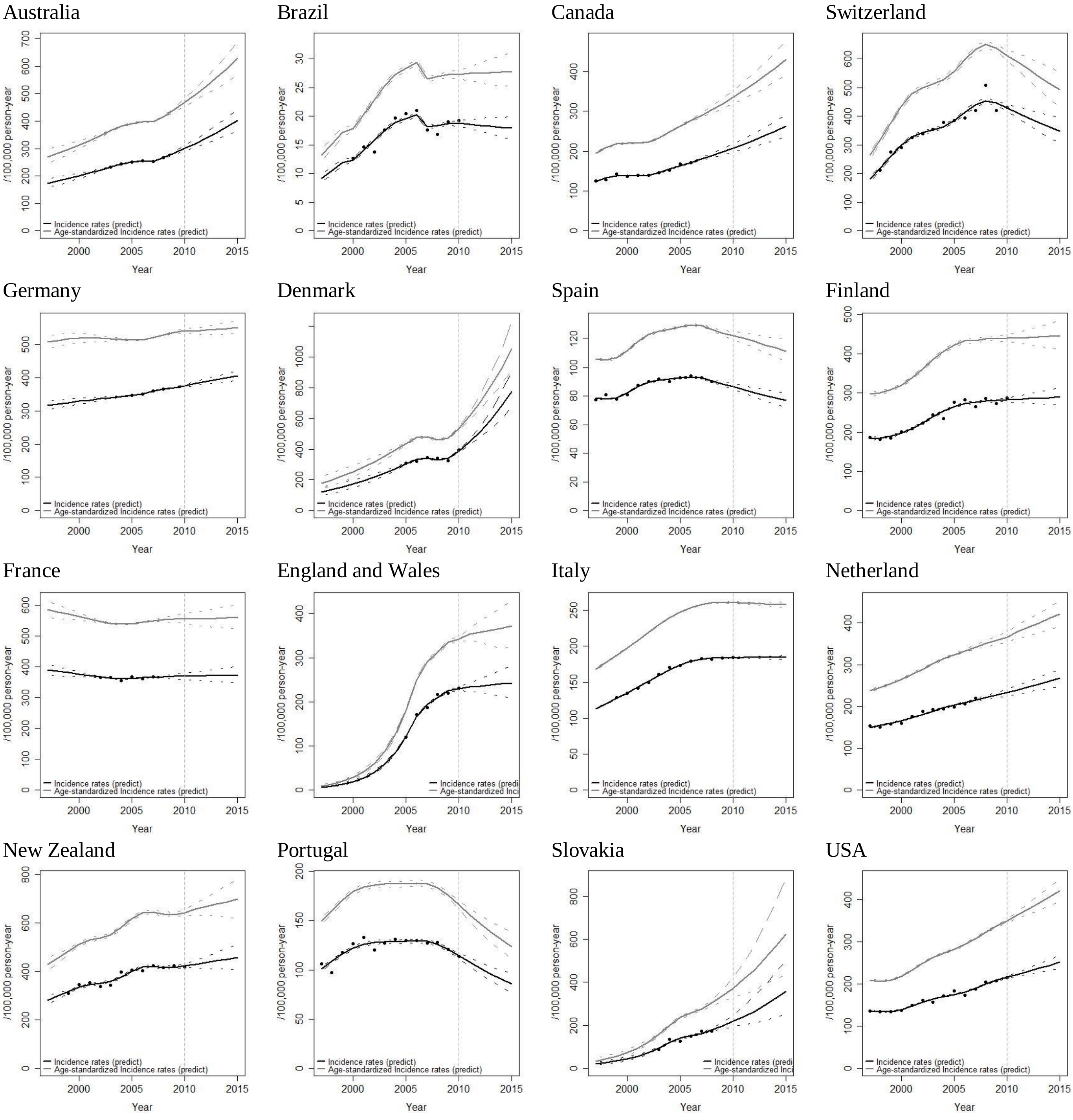


Table 1 and 2 represent, respectively for women and men, the estimated and projected absolute and relative change per year (95% confidence interval, 95%CI) in the THA trend by country between each turning point or break in growth (or decline) velocity in the period 1997–2015 (Supplementary figure 1 and 2 shows the geographical distribution of the estimated and projected relative change per year in each period: 1997-2000, 2000-2005, 2005-2010 and 2010-2015, if constant rate of change was assumed within each period). A significant reduction per year was observed in countries like Brazil (2006–2007: -10.7% per year), Portugal (2007–2010: -3.8% per year) and Switzerland (2008–2010: -2.7% per year) in men and Brazil (2005–2008: -8.1% per year), Switzerland (2008–2010: -5.4% per year), Portugal (2006–2010: -2.5% per year), Italy (2006–2010: -1.1% per year), Spain (2003–2010: -0.8% per year), France (1997–2010: -0.6% per year) and the Netherlands (2004–2010: -0.4% per year) in women. An abrupt increase per year (>10%) was observed in countries like Switzerland (1997–2008: 10.6% per year), Denmark (1997–2006: 16.6% per year) and (2009–2010: 13.2% per year), Slovakia (1997–2010: 70.9% per year) and England and Wales (1997–2010: 272.3% per year) in men and Switzerland (1997–2008: 11.9% per year), Denmark (1997–2006: 21.1% per year and 2009–2010: 15.2% per year), Brazil (1997–2005: 21.5% per year), Slovakia (1997–2010: 42.3% per year) and England and Wales (1997–2010: 329.9% per year) in women. We projected a significant reduction in incidence of THA between 2010 and 2015 in countries like Portugal (-5.2% per year), Switzerland (-4% per year) and Spain (-2.4% per year) in men and Switzerland (-8.4% per year), Portugal (-3.5% per year) and Italy (-1.8% per year) in women; and a significant increase in countries like the Netherlands (2.9% per year), the USA (3.5% per year), Canada (5.1% per year), Australia (6.6% per year) and Denmark (18.4% per year) in men and Brazil (6.7% per year), Australia (7.1% per year), the USA (7.3 (95%CI 5.26, 9.45)), Slovakia (11.56 (95%CI 1.73, 25.18)) and Denmark (23% per year) in women.

**Table 1 – Estimated and projected absolute and relative change per year (95% confidence interval) in crude and age-standardized incidence rates in women by country between 1997 and 2015**

| | | CIR | | ASIR | |
|---|---|---|---|---|---|
| Country | Period | Absolute change per year (95%CI) | Relative change per year (95%CI) | Absolute change per year (95%CI) | Relative change per year (95%CI) |
| Australia | 1997 – 2010* | 10.11 (8.64, 11.44) | 5.12 (4.07, 6.2) | 16.47 (14.55, 18.52) | 5.68 (4.69, 6.86) |
| | 2010 – 2015* | 24.85 (14.67, 35.17) | 7.09 (4.16, 10.18) | 38.3 (24.58, 54.68) | 7.1 (4.47, 10.28) |
| Brazil | 1997 – 2005* | 2.27 (2.12, 2.38) | 21.46 (18.54, 24.36) | 3.21 (3.01, 3.39) | 21.16 (18.42, 24.49) |
| | 2005 – 2008* | -2.32 (-2.53, -2.11) | -8.09 (-8.72, -7.46) | -3.19 (-3.5, -2.88) | -7.81 (-8.47, -7.16) |
| | 2008 – 2010* | 0.99 (0.64, 1.38) | 4.54 (2.91, 6.44) | 1.25 (0.79, 1.78) | 4.03 (2.51, 5.76) |
| | 2010 – 2015* | 1.67 (0.67, 2.91) | 6.67 (2.64, 11.67) | 2.11 (0.82, 3.75) | 5.91 (2.26, 10.61) |
| Canada | 1997 – 2010* | 4.12 (3.28, 4.98) | 2.52 (2.01, 3.06) | 7.59 (6.26, 8.91) | 3.16 (2.6, 3.72) |
| | 2010 – 2015 | 4.39 (-2.66, 11.97) | 1.98 (-1.18, 5.5) | 7.43 (-3.19, 19.17) | 2.14 (-0.88, 5.64) |
| Switzerland | 1997 – 2008* | 19.91 (18.53, 21.2) | 11.86 (10.52, 13.31) | 27.33 (25.4, 29.27) | 12.1 (10.68, 13.51) |
| | 2008 – 2010* | -25.74 (-34.89, -16.35) | -5.39 (-7.16, -3.48) | -35.18 (-47.03, -20.86) | -5.39 (-7.13, -3.27) |
| | 2010 – 2015* | -32.35 (-43.43, -18.95) | -8.39 (-11.08, -5.05) | -43.16 (-60.43, -25.61) | -8.16 (-11.04, -4.82) |
| Germany | 1997 – 2010* | 5.29 (4.46, 6.11) | 1.23 (1.01, 1.44) | 5.9 (4.83, 6.98) | 0.99 (0.79, 1.2) |
| | 2010 – 2015 | 2.71 (-0.17, 5.85) | 0.54 (-0.03, 1.17) | 6.45 (2.41, 10.36) | 0.95 (0.35, 1.54) |
| Denmark | 1997 – 2006* | 15.03 (13.85, 16.04) | 21.11 (16.01, 26.99) | 19.88 (18.25, 21.3) | 20.39 (15.54, 26.51) |
| | 2006 – 2009* | 1.71 (0.34, 3.13) | 0.75 (0.15, 1.4) | 0.29 (-1.68, 2.01) | 0.09 (-0.54, 0.66) |
| | 2009 – 2010* | 35.25 (29.92, 40.42) | 15.22 (12.82, 17.55) | 45.39 (38.09, 52.76) | 14.62 (12.12, 17.16) |
| | 2010 – 2015* | 71.97 (53.43, 91.15) | 22.96 (17.02, 29.37) | 89.33 (68.79, 113.65) | 21.4 (16.31, 27.85) |
| Spain | 1997 – 2003* | 0.6 (0.5, 0.72) | 0.69 (0.57, 0.82) | 1.28 (1.13, 1.43) | 1.15 (1.01, 1.29) |
| | 2003 – 2010* | -0.85 (-1.03, -0.66) | -0.83 (-1.02, -0.65) | -0.62 (-0.89, -0.35) | -0.47 (-0.67, -0.27) |
| | 2010 – 2015 | -0.12 (-1.06, 0.8) | -0.12 (-1.1, 0.84) | -0.19 (-1.48, 1.09) | -0.15 (-1.14, 0.87) |
| Finland | 1997 – 2010* | 6.4 (5.57, 7.22) | 2.68 (2.29, 3.06) | 9.6 (8.52, 10.69) | 2.84 (2.48, 3.21) |

| | | | | | |
|---|---|---|---|---|---|
| | 2010 – 2015 | 2.05 (-7.28, 12.56) | 0.63 (-2.22, 3.94) | 2.73 (-10.72, 17.2) | 0.59 (-2.29, 3.81) |
| France | 1997 – 2010* | -3.12 (-4.72, -1.42) | -0.61 (-0.89, -0.29) | -2.77 (-4.95, -0.52) | -0.39 (-0.68, -0.08) |
| | 2010 – 2015 | -5.14 (-12.17, 2.07) | -1.09 (-2.54, 0.44) | -4.82 (-15.2, 5.18) | -0.73 (-2.27, 0.78) |
| England and Wales | 1997 – 2010* | 23.69 (23.31, 24.03) | 329.93 (255.19, 414.39) | 34.19 (33.66, 34.74) | 349.45 (278.53, 443.91) |
| | 2010 – 2015 | 4.07 (-6.94, 17.24) | 1.28 (-2.19, 5.42) | 6.64 (-9.62, 25.95) | 1.43 (-2.07, 5.63) |
| Italy | 1997 – 2006* | 4.42 (4.32, 4.51) | 2.47 (2.4, 2.54) | 5.29 (5.15, 5.43) | 2.16 (2.09, 2.23) |
| | 2006 – 2010* | -2.67 (-2.87, -2.47) | -1.08 (-1.16, -1) | -2.2 (-2.46, -1.94) | -0.68 (-0.76, -0.6) |
| | 2010 – 2015* | -4.23 (-4.83, -3.63) | -1.83 (-2.08, -1.57) | -4.36 (-5.19, -3.46) | -1.41 (-1.68, -1.12) |
| Netherland | 1997 – 2004* | 3.57 (2.95, 4.18) | 0.96 (0.79, 1.12) | 7.02 (6.13, 7.89) | 1.32 (1.15, 1.49) |
| | 2004 – 2010* | -1.53 (-2.82, -0.26) | -0.36 (-0.66, -0.06) | -1.13 (-2.97, 0.67) | -0.18 (-0.47, 0.11) |
| | 2010 – 2015 | -2.42 (-6.65, 2.11) | -0.58 (-1.58, 0.51) | -0.74 (-7.38, 7.25) | -0.12 (-1.16, 1.17) |
| New Zealand | 1997 – 2008* | 9.66 (8.35, 11.01) | 3.09 (2.57, 3.69) | 16.15 (14.25, 17.89) | 3.7 (3.12, 4.28) |
| | 2008 – 2010 | -1.33 (-6.1, 3.48) | -0.3 (-1.39, 0.8) | -2.2 (-10.29, 5.47) | -0.34 (-1.56, 0.85) |
| | 2010 – 2015 | -3.21 (-12.52, 7.24) | -0.74 (-2.82, 1.68) | -3.09 (-17, 11.95) | -0.48 (-2.58, 1.83) |
| Portugal | 1997 – 2006* | 1.35 (1.11, 1.59) | 1.47 (1.18, 1.75) | 1.6 (1.27, 1.91) | 1.24 (0.97, 1.51) |
| | 2006 – 2010* | -3.03 (-3.68, -2.35) | -2.49 (-3.01, -1.95) | -4.06 (-5.05, -3.19) | -2.44 (-3.02, -1.93) |
| | 2010 – 2015* | -3.65 (-5.61, -1.72) | -3.46 (-5.2, -1.65) | -5.08 (-7.65, -2.46) | -3.52 (-5.26, -1.74) |
| Slovakia | 1997 – 2010* | 18.54 (16.2, 20.91) | 42.29 (30.57, 58.55) | 28.36 (24.69, 32.04) | 43.23 (31.59, 60.3) |
| | 2010 – 2015* | 35.63 (5.45, 73.08) | 11.56 (1.73, 25.18) | 55.17 (10.05, 109.96) | 11.64 (1.88, 24.51) |
| USA | 1997 – 2010* | 6.33 (5.99, 6.67) | 3.67 (3.44, 3.91) | 11.81 (11.28, 12.35) | 4.8 (4.54, 5.06) |
| | 2010 – 2015* | 19.82 (14.44, 25.36) | 7.3 (5.26, 9.45) | 31.75 (23.81, 40.64) | 7.46 (5.51, 9.59) |

CIR – Crude incidence rates, ASIR – Age-standardized incidence rates, 95%CI – 95% confidence interval, *p<0.05 for trend

Table 2 – Estimated and projected absolute and relative change per year (95% confidence interval) in crude and age-standardized incidence rates in men by country between 1997 and 2015

| | | CIR | | ASIR | |
|---|---|---|---|---|---|
| Country | Period | Absolute change per year (95%CI) | Relative change per year (95%CI) | Absolute change per year (95%CI) | Relative change per year (95%CI) |
| Australia | 1997 – 2010* | 9.92 (8.47, 11.27) | 5.74 (4.52, 7.12) | 15.34 (13.08, 17.5) | 5.69 (4.48, 7.04) |
| | 2010 – 2015* | 20.88 (11.33, 31.78) | 6.58 (3.55, 10.2) | 32.58 (17.11, 49.74) | 6.57 (3.39, 10.27) |
| Brazil | 1997 – 2006* | 0.74 (0.67, 0.81) | 8.08 (6.86, 9.39) | 1.07 (0.98, 1.18) | 8.1 (6.91, 9.47) |
| | 2006 – 2007* | -2.17 (-2.68, -1.64) | -10.69 (-13.05, -8.18) | -2.9 (-3.57, -2.19) | -9.87 (-12, -7.54) |
| | 2007 – 2010* | 0.23 (0.01, 0.44) | 1.25 (0.08, 2.47) | 0.25 (-0.06, 0.55) | 0.96 (-0.22, 2.11) |
| | 2010 – 2015 | -0.19 (-0.67, 0.37) | -1.02 (-3.57, 2.02) | 0.07 (-0.67, 0.9) | 0.27 (-2.45, 3.28) |
| Canada | 1997 – 2010* | 6.45 (5.65, 7.23) | 5.19 (4.53, 5.83) | 10.74 (9.46, 12.01) | 5.52 (4.88, 6.2) |
| | 2010 – 2015* | 11.1 (3.74, 18.42) | 5.09 (1.64, 8.8) | 18.71 (7.08, 30.87) | 5.31 (1.93, 9.12) |
| Switzerland | 1997 – 2008* | 19.11 (17.86, 20.29) | 10.55 (9.5, 11.65) | 26.83 (25.12, 28.49) | 10.21 (9.21, 11.21) |
| | 2008 – 2010* | -12.12 (-19.65, -4.68) | -2.67 (-4.27, -1.05) | -18.55 (-29.17, -8.01) | -2.86 (-4.44, -1.24) |
| | 2010 – 2015* | -16.43 (-28.16, -2.94) | -4 (-6.71, -0.73) | -24.01 (-40.75, -6.98) | -4.08 (-6.75, -1.22) |
| Germany | 1997 – 2010* | 4.52 (3.38, 5.6) | 1.43 (1.02, 1.85) | 2.69 (0.98, 4.36) | 0.53 (0.19, 0.9) |
| | 2010 – 2015* | 5.91 (1.91, 9.81) | 1.54 (0.49, 2.58) | 2.9 (-2.21, 8.14) | 0.54 (-0.41, 1.52) |
| Denmark | 1997 – 2006* | 20.27 (17.88, 22.47) | 16.59 (11.72, 23.2) | 27.36 (23.66, 30.27) | 15.5 (10.72, 21.53) |
| | 2006 – 2009 | 2.42 (-0.03, 4.66) | 0.73 (-0.01, 1.4) | -0.45 (-3.9, 3.04) | -0.09 (-0.81, 0.65) |
| | 2009 – 2010* | 44.87 (35.38, 54.21) | 13.15 (10.24, 16.05) | 58.27 (45.92, 71.04) | 12.29 (9.65, 15.12) |
| | 2010 – 2015* | 81.79 (55.31, 114.06) | 18.42 (12.39, 26.02) | 109.43 (70.76, 151.67) | 17.78 (11.27, 24.73) |
| Spain | 1997 – 2010* | 0.62 (0.47, 0.78) | 0.79 (0.59, 1) | 1.24 (1, 1.48) | 1.17 (0.94, 1.4) |
| | 2010 – 2015* | -2.01 (-3.3, -0.54) | -2.36 (-3.87, -0.65) | -2.13 (-4.1, -0.12) | -1.77 (-3.38, -0.1) |
| Finland | 1997 – 2010* | 7.69 (7.18, 8.21) | 4.2 (3.86, 4.56) | 11.04 (10.23, 11.9) | 3.72 (3.38, 4.08) |
| | 2010 – 2015 | 1.92 (-3.74, 8.26) | 0.67 (-1.32, 2.91) | 0.99 (-7.8, 10.61) | 0.22 (-1.74, 2.38) |

| | | | | | |
|---|---|---|---|---|---|
| France | 1997 – 2010 | -1.57 (-3.27, 0.05) | -0.4 (-0.8, 0.01) | -2.34 (-4.69, 0.06) | -0.4 (-0.77, 0.01) |
| | 2010 – 2015 | 1.14 (-6.11, 8.4) | 0.31 (-1.6, 2.35) | 1.42 (-9.27, 13.06) | 0.26 (-1.66, 2.4) |
| | 1997 – 2010* | 17.19 (16.87, 17.51) | 272.25 (205.02, 348.17) | 25.57 (25.14, 26.05) | 271.64 (210.02, 346.5) |
| England and Wales | 2010 – 2015 | 2.55 (-5.96, 12.56) | 1.11 (-2.55, 5.39) | 5.16 (-9.25, 20.38) | 1.46 (-2.61, 5.79) |
| Italy | 1997 – 2010* | 5.42 (5.32, 5.52) | 4.79 (4.66, 4.92) | 7.15 (7.01, 7.3) | 4.25 (4.14, 4.38) |
| | 2010 – 2015 | -0.11 (-0.82, 0.62) | -0.06 (-0.44, 0.34) | -0.63 (-1.65, 0.45) | -0.24 (-0.64, 0.17) |
| Netherland | 1997 – 2010* | 6.41 (5.76, 7.07) | 4.28 (3.83, 4.75) | 9.81 (8.83, 10.85) | 4.12 (3.69, 4.58) |
| | 2010 – 2015* | 6.86 (1.4, 13.14) | 2.86 (0.57, 5.56) | 10.55 (1.72, 19.28) | 2.77 (0.45, 5.2) |
| New Zealand | 1997 – 2010* | 11.04 (9.57, 12.45) | 3.92 (3.22, 4.7) | 16.56 (14.15, 18.81) | 3.87 (3.13, 4.67) |
| | 2010 – 2015 | 7.14 (-6.07, 21.52) | 1.65 (-1.41, 5.07) | 10.71 (-8.46, 31.48) | 1.63 (-1.28, 4.79) |
| Portugal | 1997 – 2002* | 1.01 (0.74, 1.28) | 1.01 (0.72, 1.3) | 1.31 (0.89, 1.73) | 0.88 (0.58, 1.19) |
| | 2002 – 2007 | 0.16 (-0.39, 0.75) | 0.13 (-0.3, 0.59) | 0.22 (-0.65, 1.05) | 0.12 (-0.34, 0.57) |
| | 2007 – 2010* | -4.92 (-6.04, -3.8) | -3.82 (-4.65, -2.96) | -7.09 (-8.79, -5.4) | -3.79 (-4.65, -2.89) |
| | 2010 – 2015* | -5.56 (-8.09, -2.66) | -5.18 (-7.31, -2.52) | -8.18 (-11.86, -4.14) | -5.25 (-7.58, -2.68) |
| Slovakia | 1997 – 2010* | 15.27 (13.15, 17.53) | 70.87 (47.37, 107.87) | 26.01 (22.59, 29.61) | 75.64 (50.47, 107.76) |
| | 2010 – 2015 | 29.46 (-1.29, 68.11) | 12.39 (-0.51, 30.63) | 51.84 (3.62, 121.56) | 12.63 (0.85, 30.84) |
| USA | 1997 – 2010* | 6.13 (5.88, 6.38) | 4.49 (4.27, 4.72) | 10.73 (10.35, 11.17) | 5.13 (4.91, 5.39) |
| | 2010 – 2015 | 7.67 (3.45, 11.98) | 3.46 (1.55, 5.48) | 7.8, 22.15) | 4 (2.13, 6.07) |

CIR – Crude incidence rates
ASIR – Age-standardized incidence rates
95%CI – 95% confidence interval
*p<0.05 for trend

Table 3 represents the estimated and projected CIR and ASIR for women and men respectively, for the first year (1997), middle years (2000 and 2005), last year (2010) and last forecast year (2015). In 2000, we estimated that the crude incidence was lower in countries like Brazil, Germany, Slovakia, and Spain for both sexes varying between 12.4 (95% CI 12.0; 12.8) and 82.4 (95%CI 82.0; 83.0) for men and between 13.8 (95% CI 13.4; 14.1) and 94.0 (95%CI 93.6; 94.4) for women per 100,000 person-year; and that incidence was higher in countries like France, New Zealand, Germany, and Switzerland for men and in countries like France, Germany, Netherland and New Zealand for women; varying between 298.8 (95%CI 293.1; 305.0) and 376.5 (95%CI 368.6; 384.1) for men and between 341.4 (95%CI 336.7; 346.3) and 507.8 (95%CI 500.3; 516.6) for women. Countries like the USA and the Netherlands for men and USA and Italy for women remained in the middle position of the crude incidence ranking of THA in 2000. Men had a lower incidence of THA compared to women in almost all of the countries, although, in Denmark, Portugal, and Switzerland, men had a higher incidence of THA compared to women at 62%, 11% and 5% higher, respectively (Table 3).

**Table 3 – Estimated and projected crude and age-standardized incidence rates (95% confidence interval) in total hip arthroplasties by country and sex between 1997 and 2015**

| | | | Year | | | | |
|---|---|---|---|---|---|---|---|
| Measure | Sex | Country | 1997 | 2000 | 2005 | 2010 | 2015 |
| CIR (95%CI) | Women | Australia | 197.49 (181.56, 214.57) | 223.97 (214.68, 233.1) | 271.57 (270, 273.15) | 328.38 (319.39, 337.61) | 449.01 (412.87, 490.12) |
| | | Brazil | 10.59 (9.63, 11.61) | 13.77 (13.42, 14.13) | 28.66 (28.16, 29.17) | 23.7 (23.07, 24.24) | 32.04 (28.1, 36.58) |
| | | Canada | 163.3 (161.53, 165.09) | 175.46 (174.11, 176.71) | 198.22 (196.74, 199.74) | 216.95 (205.1, 228.15) | 239.48 (214.43, 268.17) |
| | | Switzerland | 168.11 (157.84, 179.34) | 284.94 (277.3, 291.67) | 370.83 (361.8, 379.69) | 426.48 (412.99, 441.47) | 256.92 (212.85, 305.96) |
| | | Germany | 432.8 (422.75, 444.25) | 454.01 (447.28, 460.84) | 484.8 (483.94, 485.72) | 501.55 (498.06, 504.93) | 514.89 (504.58, 525.39) |
| | | Denmark | 71.68 (58.16, 87.98) | 106.3 (93.33, 120.99) | 203.38 (199.71, 207.39) | 266.99 (262.51, 271.58) | 598.79 (531.73, 680.87) |
| | | Spain | 87.8 (87.19, 88.39) | 94.01 (93.61, 94.39) | 99.72 (99.35, 100.1) | 95.63 (94.36, 97.05) | 94.99 (91.43, 98.47) |
| | | Finland | 238.96 (232.75, 245.17) | 248.3 (243.95, 252.56) | 300.64 (295.93, 305.56) | 322.38 (314.06, 330.33) | 332.56 (298.37, 371.61) |
| | | France | 513.85 (495.51, 533.33) | 507.84 (500.34, 516.57) | 494.22 (492.83, 495.64) | 474.99 (464.18, 485.93) | 448.08 (425.31, 473.12) |
| | | England and Wales | 7.22 (5.63, 9.1) | 23.05 (20.07, 26.82) | 162.31 (159.84, 164.73) | 315.13 (310.67, 319.67) | 336.7 (292.96, 390.33) |
| | | Italy | 178.56 (177.46, 179.6) | 206.03 (205.6, 206.44) | 244.17 (243.77, 244.55) | 235.92 (235.25, 236.58) | 214.58 (212.47, 217.01) |
| | | Netherland | 372.02 (370.02, 374.25) | 375.93 (374.63, 377.25) | 429.34 (427.76, 430.84) | 418.51 (411.58, 425.93) | 405.85 (390.98, 422.06) |
| | | New Zealand | 311 (296.84, 328.2) | 341.43 (336.67, 346.31) | 412.67 (407.04, 418.4) | 436.92 (428.46, 445.73) | 421.42 (386.29, 458.99) |
| | | Portugal | 92.13 (90.13, 94.09) | 110.08 (108.68, 111.61) | 121.8 (120.34, 123.3) | 109.54 (107.25, 111.59) | 90.58 (83.31, 98.4) |
| | | Slovakia | 43.72 (33.23, 55.96) | 74.26 (64.67, 85.24) | 173.84 (169.32, 178.19) | 283.62 (256.28, 314.47) | 455.4 (339.97, 611.67) |
| | | USA | 172.68 (170.24, 175.22) | 177.58 (175.67, 179.41) | 216.13 (214.3, 218.03) | 255.01 (251.56, 258.68) | 352.33 (331.51, 373.66) |
| | Men | Australia | 172.79 (157.97, 188.54) | 200.12 (190.33, 211.64) | 250.24 (248.52, 251.95) | 301.99 (292.39, 311.72) | 402.7 (365.37, 445.88) |
| | | Brazil | 9.15 (8.47, 9.89) | 12.38 (11.99, 12.76) | 19.58 (19.28, 19.88) | 18.77 (18.25, 19.32) | 17.89 (15.99, 19.92) |
| | | Canada | 124.08 (122.57, 125.64) | 139.04 (138, 140.1) | 163.51 (162.29, 164.65) | 207.55 (198.17, 218.34) | 261.44 (235.5, 290.2) |
| | | Switzerland | 180.9 (172.79, 189.86) | 298.83 (293.1, 304.98) | 384.52 (377.71, 391.21) | 429.26 (416.79, 441.55) | 346.75 (304.03, 391.07) |
| | | Germany | 315.32 (302.99, 329.72) | 328.67 (319.64, 337.31) | 346.43 (345.58, 347.39) | 374.88 (370.67, 379.06) | 405.58 (390.79, 420.86) |
| | | Denmark | 121.75 (96.86, 154.18) | 172.36 (148.65, 199.63) | 304.04 (297.32, 310.63) | 386.03 (378.29, 393.73) | 776.91 (675.08, 889.83) |
| | | Spain | 78.71 (78.03, 79.43) | 82.44 (81.96, 82.9) | 92.72 (92.24, 93.2) | 86.8 (84.76, 88.9) | 76.79 (72.1, 81.73) |
| | | Finland | 183.06 (178.94, 187.28) | 197.11 (194.48, 199.85) | 265.26 (262.13, 268.58) | 283.36 (277.95, 288.94) | 290.38 (269.36, 314.69) |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | France | 390.97 (373.77, 407.61) | 376.5 (368.57, 384.05) | 362.32 (360.75, 363.93) | 370.4 (359.08, 381.19) | 374.38 (346.69, 400.51) |
| | | England and Wales | 6.39 (4.97, 8.08) | 19.22 (16.68, 22.45) | 121.13 (119.3, 123.15) | 229.92 (226.36, 233.46) | 242.56 (206.15, 283.31) |
| | | Italy | 113.23 (112.15, 114.24) | 135.28 (134.85, 135.7) | 173.87 (173.47, 174.28) | 183.7 (182.95, 184.46) | 184.31 (181.76, 187.26) |
| | | Netherland | 149.67 (147.48, 151.75) | 166.5 (164.99, 168.01) | 203.46 (201.79, 205.11) | 233.07 (224.83, 241.31) | 267.5 (249.03, 288.76) |
| | | New Zealand | 280.85 (262.81, 298.16) | 334.48 (329.95, 339.59) | 401.14 (396.05, 406.45) | 423.81 (416.5, 432.56) | 456.34 (407.5, 516.12) |
| | | Portugal | 100.95 (98.28, 103.47) | 122.4 (120.42, 124.39) | 129.01 (126.93, 130.97) | 114.15 (111.41, 116.94) | 85.48 (76.74, 94.89) |
| | | Slovakia | 21.36 (15.06, 29.38) | 44.79 (37.12, 53.37) | 139.9 (136.06, 143.48) | 219.08 (194.77, 246.72) | 361.16 (245.05, 517.43) |
| | | USA | 136.7 (134.9, 138.41) | 139.26 (138.1, 140.51) | 174.91 (173.39, 176.39) | 216.33 (213.53, 219.03) | 251.93 (235.54, 267.76) |
| ASIR (95%CI) | Women | Australia | 290.28 (270.22, 314.46) | 334.25 (319.43, 349.07) | 413.49 (410.93, 415.98) | 504.62 (489.96, 519.19) | 690.69 (632.12, 750.39) |
| | | Brazil | 15.11 (13.79, 16.51) | 19.53 (19.06, 20.07) | 40.79 (40.03, 41.59) | 33.77 (32.96, 34.7) | 44.26 (38.65, 50.3) |
| | | Canada | 240.34 (237.69, 242.91) | 262.98 (261.07, 264.86) | 306.8 (304.5, 308.82) | 338.97 (322.07, 356.36) | 376.88 (338.41, 421.49) |
| | | Switzerland | 226.21 (213.35, 240.51) | 385.19 (376.37, 395.17) | 505.82 (495.14, 517.5) | 581.76 (561.53, 600.69) | 355.67 (296.85, 422.81) |
| | | Germany | 595.53 (580.87, 609.47) | 627.14 (617.95, 636.13) | 644.83 (643.61, 646.05) | 671.98 (667.51, 676.44) | 702.82 (688.91, 716.7) |
| | | Denmark | 98.16 (80.23, 118.57) | 146.15 (128.19, 166) | 279.58 (274.53, 285.16) | 355.76 (350.06, 361.65) | 775.15 (685.82, 880.29) |
| | | Spain | 111.3 (110.58, 112.1) | 120.16 (119.65, 120.65) | 130.86 (130.35, 131.36) | 127.87 (126, 129.74) | 126.53 (122.18, 131.55) |
| | | Finland | 337.85 (328.6, 346.71) | 355.6 (349.49, 361.77) | 431.07 (424.51, 437.72) | 461.67 (450.84, 473.46) | 478.63 (428.2, 531.69) |
| | | France | 704.66 (679.54, 731.46) | 696.25 (685.14, 706.82) | 676.5 (674.61, 678.53) | 667.81 (652.83, 683.41) | 643.46 (609.92, 679.03) |
| | | England and Wales | 9.82 (7.82, 12.19) | 31.78 (27.57, 37.09) | 229.5 (226.12, 233.07) | 454.27 (447.89, 461.08) | 485 (421.3, 553.86) |
| | | Italy | 244.72 (243.35, 246.16) | 278.19 (277.63, 278.74) | 319.98 (319.45, 320.48) | 313.46 (312.58, 314.3) | 290.55 (287.64, 293.46) |
| | | Netherland | 533.15 (530.09, 536.37) | 545.34 (543.41, 547.36) | 635.32 (633.15, 637.58) | 624.72 (614.3, 635.96) | 625.58 (601.74, 652.51) |
| | | New Zealand | 436.1 (415.15, 456.58) | 486.66 (479.65, 493.19) | 606.51 (598.52, 614.02) | 646.45 (634.06, 658.98) | 635.3 (584.29, 690.89) |
| | | Portugal | 128.98 (126.12, 131.72) | 152.55 (150.41, 154.69) | 166.15 (164.2, 168.09) | 149.67 (146.84, 152.68) | 123.17 (113.6, 133.14) |
| | | Slovakia | 65.4 (49.79, 84.53) | 111.29 (96.78, 128.37) | 265.29 (258.74, 271.83) | 434.45 (393.62, 482.64) | 696.9 (513.92, 925.75) |
| | | USA | 246.34 (242.66, 249.88) | 261.29 (258.66, 263.72) | 332.99 (330.22, 335.72) | 399.93 (394.56, 405.51) | 554.03 (522.4, 586.5) |
| | Men | Australia | 269.4 (245.33, 294.95) | 313.76 (298.05, 328.22) | 391.21 (388.6, 393.74) | 467.84 (453.85, 482.61) | 628.6 (568, 694.83) |
| | | Brazil | 13.23 (12.13, 14.35) | 17.85 (17.36, 18.37) | 28.33 (27.87, 28.8) | 27.21 (26.53, 27.96) | 27.77 (25, 30.91) |
| | | Canada | 194.63 (192.16, 196.78) | 219.94 (218.28, 221.54) | 262.94 (261.02, 264.71) | 333.78 (317.84, 351.76) | 429.91 (386.26, 475.32) |
| | | Switzerland | 263.38 (250.27, 276.16) | 434.99 (426.63, 443.36) | 556.6 (546.59, 567.03) | 611.75 (593.94, 629.35) | 490.29 (432.75, 564.96) |
| | | Germany | 505.86 (483.88, 529.36) | 519.23 (505.05, 533.04) | 512.16 (510.79, 513.56) | 541.92 (536.08, 548) | 551.01 (530.61, 570.73) |

| | | | | | |
|---|---|---|---|---|---|
| Denmark | 176.05 (141, 222.62) | 253.82 (217.02, 291.93) | 436.52 (427.1, 445.54) | 531.74 (521.49, 542.39) | 1053.23 (903.52, 1219.95) |
| Spain | 106.09 (105.13, 107.06) | 111.83 (111.16, 112.49) | 128.53 (127.83, 129.23) | 122.29 (119.47, 124.87) | 111.69 (104.66, 118.94) |
| Finland | 296.92 (290.41, 303.43) | 320.13 (315.65, 324.33) | 421.83 (416.81, 426.79) | 440 (431.68, 448.84) | 446.08 (412.49, 482.8) |
| France | 586.91 (558.69, 612.92) | 563.29 (551.22, 574.53) | 539.83 (537.33, 542.26) | 556.6 (540.44, 574.71) | 561.64 (521.14, 600.83) |
| England and Wales | 9.34 (7.39, 11.75) | 28.59 (24.19, 33.58) | 180.68 (177.67, 183.73) | 341.76 (337.04, 346.88) | 371.08 (320.56, 434.88) |
| Italy | 168.2 (166.6, 169.89) | 198.07 (197.44, 198.67) | 247.31 (246.72, 247.92) | 261.16 (260.16, 262.2) | 257.78 (254.29, 261.22) |
| Netherland | 237.82 (234.51, 241.4) | 265.51 (263.12, 267.81) | 324.35 (321.81, 326.85) | 365.18 (352.47, 376.9) | 420.97 (391.3, 456) |
| New Zealand | 427.02 (401.74, 452.96) | 511.09 (504.06, 519.14) | 618.15 (609.05, 626.63) | 642.98 (629.74, 654.06) | 698.36 (625.31, 776.6) |
| Portugal | 149.36 (145.83, 153.27) | 179.41 (176.8, 182.5) | 187.14 (184.22, 190.16) | 166.21 (162.12, 170.38) | 122.99 (109.93, 137.81) |
| Slovakia | 34.51 (24.45, 48.82) | 73.25 (60.41, 89.33) | 236.46 (229.68, 243.37) | 375.28 (328.61, 422.13) | 625.72 (431.75, 885.66) |
| USA | 209.23 (206.48, 211.94) | 218.04 (216.13, 219.98) | 281.5 (279.05, 284.09) | 348.69 (343.92, 352.9) | 421.33 (394.42, 449.71) |

CIR – Crude incidence rates
ASIR – Age-standardized incidence rates
95%CI – 95% confidence interval

In 2005, the middle period between 2000 and 2010, the ranking of countries with lower incidence hardly changed compared to 2000, a replacement of Slovakia by Portugal was observed in the ranking, but the others maintained the four lowest positions: Brazil, Spain and Germany for both sexes, varying between 19.6 (95%CI 19.3; 19.9) and 129.0 (95%CI 126.9; 131.0) for men and between 28.7 (95%CI 28.2; 29.2) and 162.3 (95%CI 159.8; 164.7) for women. Also, the ranking of countries with higher incidence barely changed compared to 2000; the four highest incidences were still observed in countries like New Zealand, Switzerland, France and Germany for men and in France, Germany, Netherland and New Zealand for women; varying between 346.4 (95%CI 345.6; 347.4) and 401.1 (95%CI 396.1; 406.5) for men and between 412.7 (95%CI 407.0; 418.4) and 494.2 (95%CI 492.8; 495.6) for women. In the middle position of the crude incidence ranking of THA were the same countries as in 2000, the USA and the Netherlands for men and the USA and Italy for women. Even though there was no significant change in ranking between 2000 and 2005, a dramatic change in magnitude of THA incidence rate was observed as higher in 2005. Denmark, Portugal and Switzerland still had a higher incidence for men than for women at 49%, 6% and 4% higher, respectively (Table 3).

In 2010, the final period of the estimated THA, the ranking position of countries with the lowest incidences did not change much compared to 2005, a replacement of Germany by Italy for men and Canada for women was observed, but the other countries maintained the three lowest positions: Brazil, Spain and Portugal; varying between 18.8 (95%CI 18.3; 19.3) and 183.7 (95%CI 183.0; 184.5) for men and between 23.7 (95%CI 23.1; 24.2) and 217.0 (95%CI 205.1; 228.2) for women. Also, the ranking of countries with higher incidence did not change significantly compared to 2005, a replacement of France by Denmark for men and of the Netherlands by Switzerland for women in the ranking was observed, but the others maintained the four highest positions: Switzerland, New Zealand, and Germany for men and Germany, France and New Zealand for women; varying between 374.9 (95%CI 370.7; 379.1) and 429.3 (95%CI 416.8; 441.6) for men and between 426.5 (95%CI 413.0; 441.5) and 501.6 (95%CI 498.1; 504.9) for women. In the middle position of the ranking of THA incidence rates were countries like England and Wales and the Netherlands for men and Slovakia and England and

Wales for women. Denmark, Portugal, and Switzerland still had a higher incidence in men than in women at 45%, 4% and 1% higher in 2010, respectively (Table 3).

We have projected that in 2015 the crude incidence will maintain lower in countries like Brazil, Spain, Portugal and Italy for both sexes, varying between 17.9 (95%CI 16.0; 19.9) and 184.3 (95%CI 181.8; 187.3) for men and between 32.0 (95%CI 28.1; 36.6) and 214.6 (95%CI 212.5; 217.0) for women and will be higher in countries like Denmark, New Zealand, Germany and Australia for men and Denmark, Germany, Slovakia and Australia for women; varying between 402.7 (95%CI 365.4; 445.9) and 776.9 (95%CI 675.1; 889.8) for men and between 449.0 (95%CI 412.9; 490.1) and 598.8 (95%CI 531.7; 680.9) for women. We have projected that in 2015 the crude incidence will be higher for women than for men in almost all of the countries, with the exception of Switzerland, Denmark, Canada and New Zealand, which will be estimated at 35%, 30%, 9% and 8% higher in men than in women, respectively (Table 3).

Figures 3 and 4 show the trend in SMR during the period of study if the population were to have the same age-structure as the USA in 1997 (supplementary figure 3 and 4 shows the geographical distribution of the SMR in 1997, 2000, 2005, 2010 and 2015). Countries with the highest SMR were France, Germany, New Zealand and the Netherlands for both sexes and those with the lowest SMR were Brazil, Spain, and Portugal for both sexes. An abrupt increase in the SMR was observed in countries like England and Wales, Denmark, and Slovakia and a marked increase in New Zealand, Australia, the USA, Canada, and Finland for both sexes and in the Netherlands for women was observed. Countries with a clear pattern of increase followed by a decrease were Switzerland, Spain, and Portugal for both sexes and Italy for women.

**Figure 3 - Trends in standard morbidity rates of total hip arthroplasties (95% confidence interval) by country in women patient (1997-2010) and projected (2010-2015)**

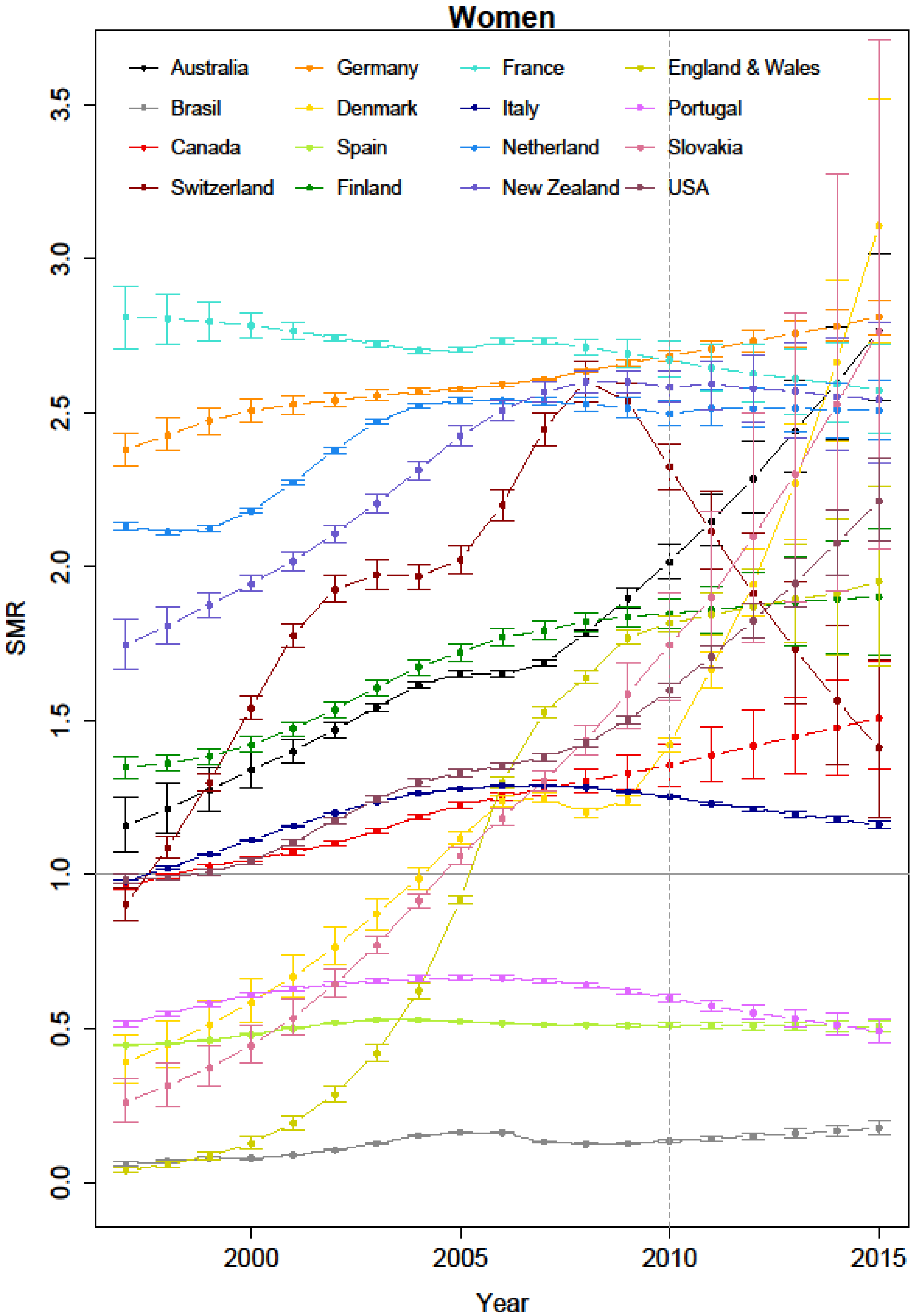


**Figure 4 - Trends in standard morbidity rates of total hip arthroplasties (95% confidence interval) by country in men patient (1997-2010) and projected (2010-2015)**

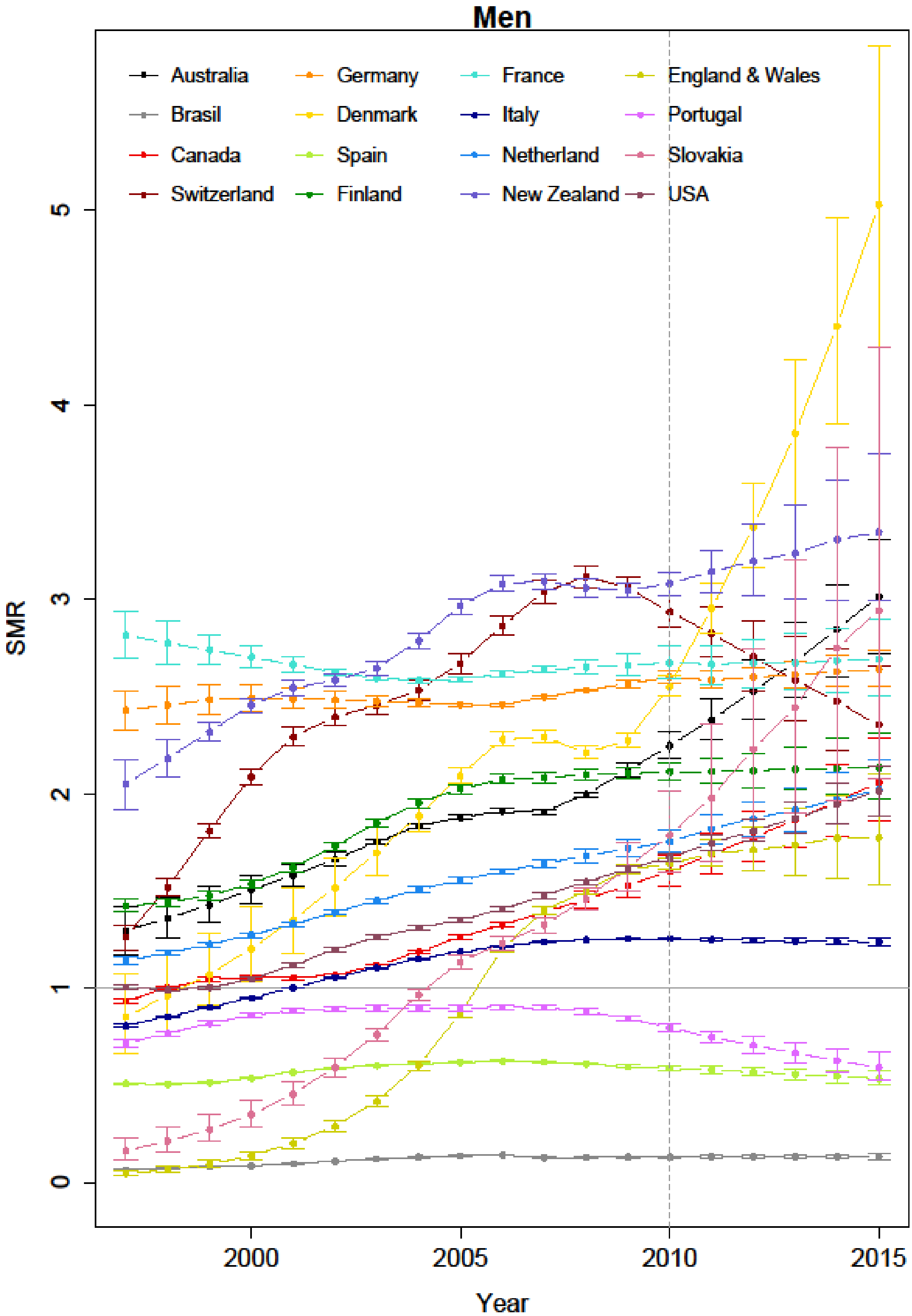


Table 4 represents the estimated and projected SMR for women and men respectively, for the first year (1997), middle years (2000 and 2005), last year (2010) and last forecast year (2015). We estimated that if the population were to have the same age-structure as the population of the USA in 1997 as in 2000, Brazil would have the lowest SMR for both sexes (men: 0.08 95%CI 0.08-0.08 and women: 0.09 95%CI 0.08-0.09) and France would have the highest SMR for both sexes (men: 2.70 95%CI 2.64-2.76 and women: 2.78 95%CI 2.74-2.83); in 2005, Brazil still had the lowest SMR for both sexes (men: 0.14 95%CI 0.13-0.14 and women: 0.16 95%CI 0.16-0.17) and New Zealand had the highest for men (2.96 95%CI 2.92-3.01) and France had the highest for women (2.7 95%CI 2.7-2.71); in 2010, Brazil still had the lowest SMR for both sexes (men: 0.13 95%CI 0.13-0.13 and women: 0.13 95%CI 0.13-0.14) and New Zealand had the highest for men (3.08 95%CI 3.02-3.14) and Germany for women (2.69 95%CI 2.67-2.7); and in 2015, the lowest SMR is projected in Brazil for both sexes (men: 0.13 95%CI 0.12-0.15 and women: 0.18 95%CI 0.15-0.2) and the highest in Denmark for both sexes (men: 5.05 95%CI 4.33-5.85 and women: 3.1 95%CI 2.74; 3.52) (Table 4).

**Table 4 – Estimated and projected standard morbidity rates (95% confidence interval) in total hip arthroplasties by country and sex between 1997 and 2015**

| | | | Year | | | | |
|---|---|---|---|---|---|---|---|
| Measure | Sex | Country | 1997 | 2000 | 2005 | 2010 | 2015 |
| SMR (95%CI) | Women | Australia | 1.16 (1.08, 1.26) | 1.34 (1.28, 1.4) | 1.65 (1.64, 1.66) | 2.02 (1.96, 2.08) | 2.76 (2.53, 3) |
| | | Brazil | 0.06 (0.06, 0.07) | 0.08 (0.08, 0.08) | 0.16 (0.16, 0.17) | 0.13 (0.13, 0.14) | 0.18 (0.15, 0.2) |
| | | Canada | 0.96 (0.95, 0.97) | 1.05 (1.04, 1.06) | 1.23 (1.22, 1.23) | 1.35 (1.29, 1.42) | 1.51 (1.35, 1.68) |
| | | Switzerland | 0.9 (0.85, 0.96) | 1.54 (1.5, 1.58) | 2.02 (1.98, 2.07) | 2.33 (2.24, 2.4) | 1.42 (1.19, 1.69) |
| | | Germany | 2.38 (2.32, 2.44) | 2.51 (2.47, 2.54) | 2.58 (2.57, 2.58) | 2.69 (2.67, 2.7) | 2.81 (2.75, 2.86) |
| | | Denmark | 0.39 (0.32, 0.47) | 0.58 (0.51, 0.66) | 1.12 (1.1, 1.14) | 1.42 (1.4, 1.45) | 3.1 (2.74, 3.52) |
| | | Spain | 0.44 (0.44, 0.45) | 0.48 (0.48, 0.48) | 0.52 (0.52, 0.53) | 0.51 (0.5, 0.52) | 0.51 (0.49, 0.53) |
| | | Finland | 1.35 (1.31, 1.39) | 1.42 (1.4, 1.45) | 1.72 (1.7, 1.75) | 1.85 (1.8, 1.89) | 1.91 (1.71, 2.13) |
| | | France | 2.82 (2.72, 2.92) | 2.78 (2.74, 2.83) | 2.7 (2.7, 2.71) | 2.67 (2.61, 2.73) | 2.57 (2.44, 2.71) |
| | | England and Wales | 0.04 (0.03, 0.05) | 0.13 (0.11, 0.15) | 0.92 (0.9, 0.93) | 1.82 (1.79, 1.84) | 1.94 (1.68, 2.21) |
| | | Italy | 0.98 (0.97, 0.98) | 1.11 (1.11, 1.11) | 1.28 (1.28, 1.28) | 1.25 (1.25, 1.26) | 1.16 (1.15, 1.17) |
| | | Netherland | 2.13 (2.12, 2.14) | 2.18 (2.17, 2.19) | 2.54 (2.53, 2.55) | 2.5 (2.46, 2.54) | 2.5 (2.41, 2.61) |
| | | New Zealand | 1.74 (1.66, 1.83) | 1.95 (1.92, 1.97) | 2.42 (2.39, 2.45) | 2.58 (2.53, 2.63) | 2.54 (2.34, 2.76) |
| | | Portugal | 0.52 (0.5, 0.53) | 0.61 (0.6, 0.62) | 0.66 (0.66, 0.67) | 0.6 (0.59, 0.61) | 0.49 (0.45, 0.53) |
| | | Slovakia | 0.26 (0.2, 0.34) | 0.44 (0.39, 0.51) | 1.06 (1.03, 1.09) | 1.74 (1.57, 1.93) | 2.79 (2.05, 3.7) |
| | | USA | 0.98 (0.97, 1) | 1.04 (1.03, 1.05) | 1.33 (1.32, 1.34) | 1.6 (1.58, 1.62) | 2.21 (2.09, 2.34) |
| | Men | Australia | 1.29 (1.18, 1.41) | 1.5 (1.43, 1.57) | 1.88 (1.86, 1.89) | 2.24 (2.18, 2.31) | 3.01 (2.72, 3.33) |
| | | Brazil | 0.06 (0.06, 0.07) | 0.09 (0.08, 0.09) | 0.14 (0.13, 0.14) | 0.13 (0.13, 0.13) | 0.13 (0.12, 0.15) |
| | | Canada | 0.93 (0.92, 0.94) | 1.05 (1.05, 1.06) | 1.26 (1.25, 1.27) | 1.6 (1.52, 1.69) | 2.06 (1.85, 2.28) |
| | | Switzerland | 1.26 (1.2, 1.32) | 2.09 (2.05, 2.13) | 2.67 (2.62, 2.72) | 2.93 (2.85, 3.02) | 2.35 (2.08, 2.71) |
| | | Germany | 2.43 (2.32, 2.54) | 2.49 (2.42, 2.56) | 2.46 (2.45, 2.46) | 2.6 (2.57, 2.63) | 2.64 (2.54, 2.74) |
| | | Denmark | 0.84 (0.68, 1.07) | 1.22 (1.04, 1.4) | 2.09 (2.05, 2.14) | 2.55 (2.5, 2.6) | 5.05 (4.33, 5.85) |
| | | Spain | 0.51 (0.5, 0.51) | 0.54 (0.53, 0.54) | 0.62 (0.61, 0.62) | 0.59 (0.57, 0.6) | 0.54 (0.5, 0.57) |
| | | Finland | 1.42 (1.39, 1.46) | 1.54 (1.51, 1.56) | 2.02 (2, 2.05) | 2.11 (2.07, 2.15) | 2.14 (1.98, 2.32) |
| | | France | 2.81 (2.68, 2.94) | 2.7 (2.64, 2.76) | 2.59 (2.58, 2.6) | 2.67 (2.59, 2.76) | 2.69 (2.5, 2.88) |
| | | England and Wales | 0.04 (0.04, 0.06) | 0.14 (0.12, 0.16) | 0.87 (0.85, 0.88) | 1.64 (1.62, 1.66) | 1.78 (1.54, 2.09) |
| | | Italy | 0.81 (0.8, 0.81) | 0.95 (0.95, 0.95) | 1.19 (1.18, 1.19) | 1.25 (1.25, 1.26) | 1.24 (1.22, 1.25) |
| | | Netherland | 1.14 (1.12, 1.16) | 1.27 (1.26, 1.28) | 1.56 (1.54, 1.57) | 1.75 (1.69, 1.81) | 2.02 (1.88, 2.19) |
| | | New Zealand | 2.05 (1.93, 2.17) | 2.45 (2.42, 2.49) | 2.96 (2.92, 3.01) | 3.08 (3.02, 3.14) | 3.35 (3, 3.72) |
| | | Portugal | 0.72 (0.7, 0.74) | 0.86 (0.85, 0.88) | 0.9 (0.88, 0.91) | 0.8 (0.78, 0.82) | 0.59 (0.53, 0.66) |

| | | | | | | |
|---|---|---|---|---|---|---|
| | Slovakia | 0.17 (0.12, 0.23) | 0.35 (0.29, 0.43) | 1.13 (1.1, 1.17) | 1.8 (1.58, 2.02) | 3 (2.07, 4.25) |
| | USA | 1 (0.99, 1.02) | 1.05 (1.04, 1.05) | 1.35 (1.34, 1.36) | 1.67 (1.65, 1.69) | 2.02 (1.89, 2.16) |

SMR – Standard morbidity rates
95%CI – 95% confidence interval

**Discussion**

This study used national data to examine differences in the temporal trend of THA between countries and the results show a general trend increase in the overall period between 1997 and 2010 (if a constant rate of change is assumed). However, this increase is not linear and different patterns have emerged: in England and Wales for both sexes, in Finland, France, Italy for men and in New Zealand for women, a pattern of increase and posterior stabilization was observed; in Switzerland, Spain and Portugal for both sexes and in Italy for women, there was a pattern of increase followed by decrease; France showed a pattern of decrease; Brazil, even with a pattern of growth since 1997, showed a period of instability in the pattern, a peak (increase-decrease) was observed around 2005. In general, a similar pattern in temporal trend was observed in both sexes and there is no agreement whether the velocity of increase or decrease is more accentuated in women or men between 1997 and 2010 (if a constant rate of change is assumed).

The observed low THA in Portugal, Spain and Italy may be an indication of low THA in some Eastern and Southern European countries and the high reported THA in Switzerland and Germany may indicate higher incidence in Northern European Countries.

France, Germany and New Zealand for both sexes and the Netherlands for women showed the highest SMR for the entire period; Brazil, Spain, and Portugal for both sexes showed the lowest SMR in the entire period. England and Wales, Denmark and Slovakia showed an abrupt increase in the SMR; New Zealand, Australia, the USA, Canada, and Finland for both sexes and the Netherlands for women showed a marked increase; and Switzerland and Portugal for both sexes and Italy for women showed a clear pattern of increase followed by a decrease.

One of the reasons for the pattern of increase in temporal trend in almost all of the countries may be due to the increased life expectancies at birth. Although, there are some studies that explore this issue and have found that increased population and aging can only explain a small part of the trend increase [17, 18]; the Dutch and Swedish studies found that only 3% and 15%, respectively, can be the consequence of changes in population age structure [16]. Another plausible reason is the reflection of improvement in surgical techniques, implant materials, designs and peri-operative care and better outcomes observed during this period, which have led to an increased demand for service and by patient [9, 19] for this procedure. Also, the higher prevalence of comorbidity, such as obesity, and the increased risk factors as well as unhealthy lifestyles that have been seen; increases the need for this intervention. By age 18, obesity becomes a reliable predictor of a need for THA sometime in the future.[7].

However, it appears that this pattern is not equal in all regions. These differences in patterns and in velocity of temporal change may be caused by differences in demographics and health care system organization, characteristics and financing between regions [19], such as differences in the number of trained orthopedic surgeons performing arthroplasties, bed and space for operations, and the existence and application of criteria for surgery [7]. Orthopedic implantation is one of the most expensive hospital procedures and with the increase of health-related costs all over the world and the restriction on economic resources, especially in certain countries, some constraint regarding this procedure naturally results and the pattern of increase followed by decrease observed in Spain and Portugal for both sexes and in Italy for women may be a reflection of this constraint, due to the fact that these countries are highly affected by economic recession.

Projections of increase for THA will have some implication for service provision, planning, and cost: cost will increase, the number of available beds will decrease and the overall number of operations that can be performed will decrease [9]. Regarding this fact, monitoring this projection is important for better planning of future health finance and resources, such as surgical and rehabilitation centers or specialist consultations. In England, there was a projected increase of THA from 2000 to 2010 of about 94 per 100,000 in women and 74 per 100,000 in men, based on projected rates [9]. However, in our data we estimated a much higher increase than the previous study; an increase of 207 in men and 288 in women per 100,000 person-year was observed. In Denmark, with a projected increase of THA from 2002 to 2010 of about 143 (95%CI 140-147) per 100,000 person-year in both sexes, we estimated an increase of 169 (95%CI 155.46, 187.27) in men and 129 (95%CI 122.82, 136.96) in women per 100,000 person-year, a

93% and 78% increase, respectively. Current projections in 2007 estimate an increase of 174% in the USA between 2005 and 2030 in the number of THA [18] and we estimated an increase between 2005 and 2010 of 108,79 (95%CI 106.94, 112.64) in men and 152,81 (95%CI 149.08, 155.74) in women per 100,000 person-year, 90% and 94% respectively; and we projected an increase between 2005 and 2015 of 121,43 (95%CI 97.88, 162.50) in men and 174,38 (95%CI 142.15, 205.59) in women, 100% and 107% respectively. It seems that these increases are archiving more than half of the rate in half of the period than what was estimated in the previous study and that the increase has been higher than what was projected.

Our study has some limitations, but also some strengths, which should be stressed. Limitations are the potential source of bias due to data collection and discrepancies between administrative registries. However, some studies show that these discrepancies have not resulted in a significant amount of source bias and this data is quite reliable [19]. Depending on the country, data comes from different organizations. Most are maintained by national orthopedic associations, others not. For instance, in England and Finland, the government institutions had this responsibility; in Canada, it was made in conjunction with the federal health authorities [10]. In the Scandinavian countries, it was made with the National Hip Arthroplasties Registries and in France with the recently installed Medical Information System, including public and private hospitals registries; in England, with the National Health Service (NHS), including private insurance payment. However, in countries like Portugal and New Zealand, the data only refers to the National Services Hospital with the exclusion of private institutions, leading to an underestimation of THA in these countries [12]. Also, different national coding systems [7] and changes in improvement in coding during the study period can lead to a higher report of comorbidities [19], which is a potential source of bias. For instance, the ICD-9-CM code used by the USA and Portugal only allows for the THA to be distinguished between partial replacement and hip revision whereas the French coding derived from the American DRG, or the OPCS4 used in England and Wales, is more detailed [12]. Not only was the collected data different, but also the aggregates in different age groups were different in one country. In Denmark, the aggregation was not possible to perform in the desired format: 45-64; 65-74; 75-84; >84; the aggregation performed was: 40-59; 60-69; 70-79; >79 which also results in bias between countries.

For predictions, it was assumed that there would be no change in the age-specific incidence rate of THA during this period, which led to an underestimated future of THA. The demographic projections may also be imprecise as constant fertility, migration, and mortality rates were assumed. The projections made only take into account past values and, most likely, some values might be too wide or too narrow to be informative. However, monitoring this projection is important in order to plan a more effective intervention program. Also, as an observational study, the association found cannot be a causal relationship.

The strength of this study was the large sample size, the long time span, the number of countries involved and the standardized methodologies. The age-standardization incidence rates were used to avoid the impact of different country age-structures in the THA incidence rates. The indirect standardization used allows us to consider the trend per country as if its population were distributed like the population in the USA in 1997 and to use the SMR as a measure to compare each country to the USA in 1997.

**Conclusions**

Our study has had a significant impact in regards to the higher variability between countries in THA incidence rates and the expected trend increase in almost every country with an alarming decrease in countries with some economic constraints, which has led us to consider that this may not be a reduction based on people’s needs, but rather an issue of cost reduction. These results can also be used for future evaluation in the forthcoming years. The increase or decrease forecasted will have a substantial effect on planning future health finance and resources, such as surgical and rehabilitation centers or specialist consultations.

**References**

1. Steel N, Melzer D, Gardener E, McWilliams B. Need for and receipt of hip and knee replacement--a national population survey. Rheumatology (Oxford). 2006;45(11):1437-41. Epub 2006/04/25.

2. Crawford RW, Murray DW. Total hip replacement: indications for surgery and risk factors for failure. Annals of the rheumatic diseases. 1997;56(8):455-7. Epub 1997/08/01.

3. Singh JA. Epidemiology of knee and hip arthroplasty: a systematic review. The open orthopaedics journal. 2011;5:80-5. Epub 2011/05/18.

4. Judge A, Welton NJ, Sandhu J, Ben-Shlomo Y. Equity in access to total joint replacement of the hip and knee in England: cross sectional study. BMJ. 2010;341:c4092. Epub 2010/08/13.

5. Callaghan JJ, Bracha P, Liu SS, Piyaworakhun S, Goetz DD, Johnston RC. Survivorship of a Charnley total hip arthroplasty. A concise follow-up, at a minimum of thirty-five years, of previous reports. The Journal of bone and joint surgery American volume. 2009;91(11):2617-21. Epub 2009/11/04.

6. Callaghan JJ, Templeton JE, Liu SS, Pedersen DR, Goetz DD, Sullivan PM, et al. Results of Charnley total hip arthroplasty at a minimum of thirty years. A concise follow-up of a previous report. The Journal of bone and joint surgery American volume. 2004;86-A(4):690-5. Epub 2004/04/08.

7. Birrell F, Johnell O, Silman A. Projecting the need for hip replacement over the next three decades: influence of changing demography and threshold for surgery. Annals of the rheumatic diseases. 1999;58(9):569-72. Epub 1999/08/25.

8. Ibrahim T, Bloch B, Esler CN, Abrams KR, Harper WM. Temporal trends in primary total hip and knee arthroplasty surgery: results from a UK regional joint register, 1991-2004. Annals of the Royal College of Surgeons of England. 2010;92(3):231-5. Epub 2010/03/13.

9. Dixon T, Shaw M, Ebrahim S, Dieppe P. Trends in hip and knee joint replacement: socioeconomic inequalities and projections of need. Annals of the rheumatic diseases. 2004;63(7):825-30. Epub 2004/06/15.

10. Kolling C, Simmen BR, Labek G, Goldhahn J. Key factors for a successful National Arthroplasty Register. The Journal of bone and joint surgery British volume. 2007;89(12):1567-73. Epub 2007/12/07.

11. Pina MF, Ribeiro AI, Santos C. Epidemiology and Variability of Orthopaedic Procedures Worldwide. European Instructional Lectures. 2011:9-19.

12. Merx H, Dreinhofer K, Schrader P, Sturmer T, Puhl W, Gunther KP, et al. International variation in hip replacement rates. Annals of the rheumatic diseases. 2003;62(3):222-6. Epub 2003/02/21.

13. Kurtz S, Mowat F, Ong K, Chan N, Lau E, Halpern M. Prevalence of primary and revision total hip and knee arthroplasty in the United States from 1990 through 2002. The Journal of bone and joint surgery American volume. 2005;87(7):1487-97. Epub 2005/07/05.

14. Wells VM, Hearn TC, McCaul KA, Anderton SM, Wigg AE, Graves SE. Changing incidence of primary total hip arthroplasty and total knee arthroplasty for primary osteoarthritis. The Journal of arthroplasty. 2002;17(3):267-73. Epub 2002/04/09.

15. Bang H, Chiu YL, Memtsoudis SG, Mandl LA, Della Valle AG, Mushlin AI, et al. Total hip and total knee arthroplasties: trends and disparities revisited. Am J Orthop (Belle Mead NJ). 2010;39(9):E95-102. Epub 2011/02/04.

16. Ostendorf M, Johnell O, Malchau H, Dhert WJ, Schrijvers AJ, Verbout AJ. The epidemiology of total hip replacement in The Netherlands and Sweden: present status and future needs. Acta orthopaedica Scandinavica. 2002;73(3):282-6. Epub 2002/07/30.

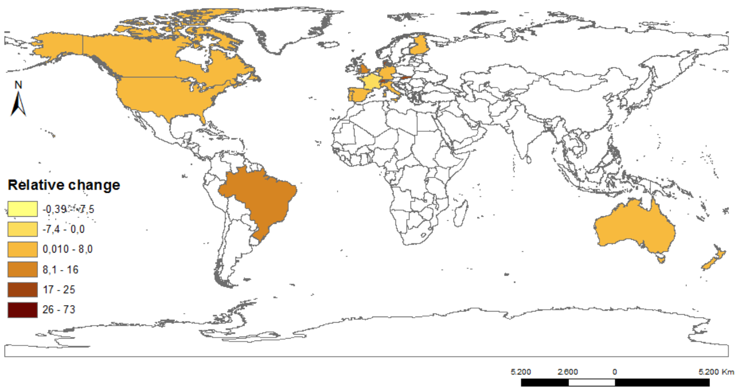
17. Liu SS, Della Valle AG, Besculides MC, Gaber LK, Memtsoudis SG. Trends in mortality, complications, and demographics for primary hip arthroplasty in the United States. International orthopaedics. 2009;33(3):643-51. Epub 2008/05/08.

18. Kurtz S, Ong K, Lau E, Mowat F, Halpern M. Projections of primary and revision hip and knee arthroplasty in the United States from 2005 to 2030. The Journal of bone and joint surgery American volume. 2007;89(4):780-5. Epub 2007/04/04.

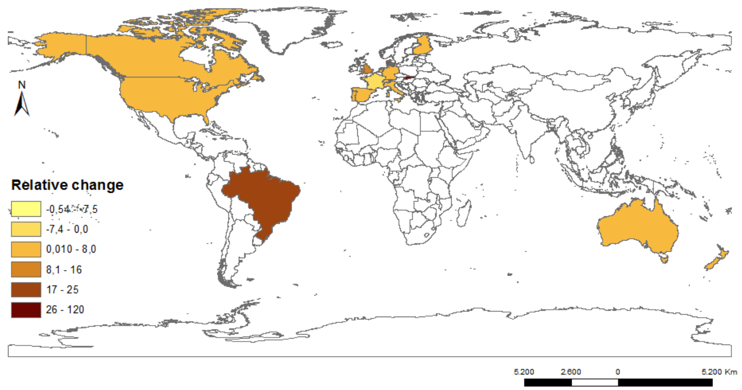
19. Jimenez-Garcia R, Villanueva-Martinez M, Fernandez-de-Las-Penas C, Hernandez-Barrera V, Rios-Luna A, Garrido PC, et al. Trends in primary total hip arthroplasty in Spain from 2001 to 2008: evaluating changes in demographics, comorbidity, incidence rates, length of stay, costs and mortality. BMC musculoskeletal disorders. 2011;12:43. Epub 2011/02/11.

**Supplementary figure 1 – Geographic distribution of the estimated and predicted absolute and relative change per year in crude incidence rates of total hip arthroplasties in women by country between 1997-2000, 2000-2005, 2005-2010 and 2010-2015**

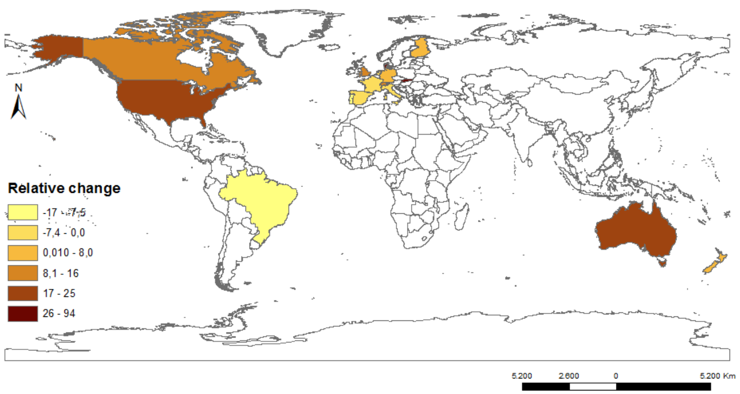
**Women 1997-2000**



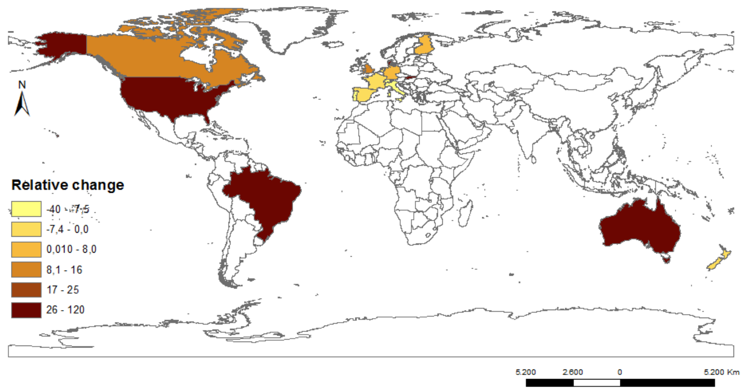

**Women 2000-2005**




**Women 2005-2010**

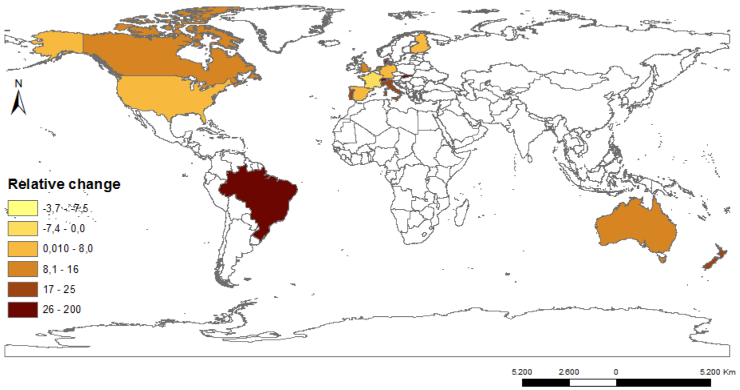



**Women 2010-2015**

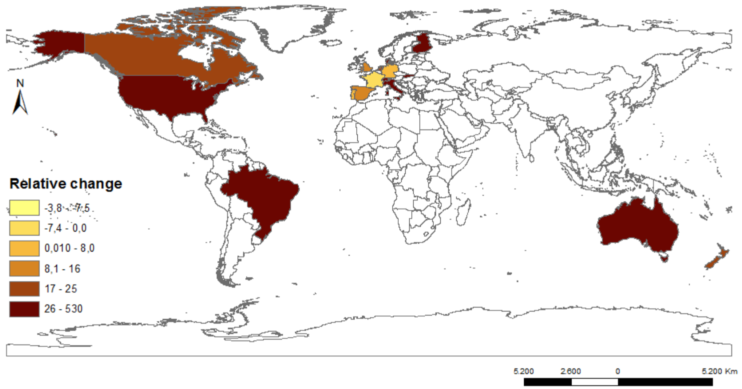


**Supplementary figure 2 – Geographic distribution of the estimated and predicted absolute and relative change per year in crude incidence rates of total hip arthroplasties in men by country between 1997-2000, 2000-2005, 2005-2010 and 2010-2015**

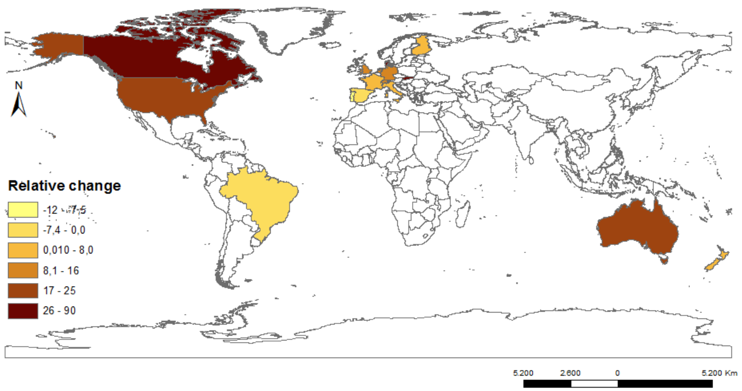
**Men 1997-2000**



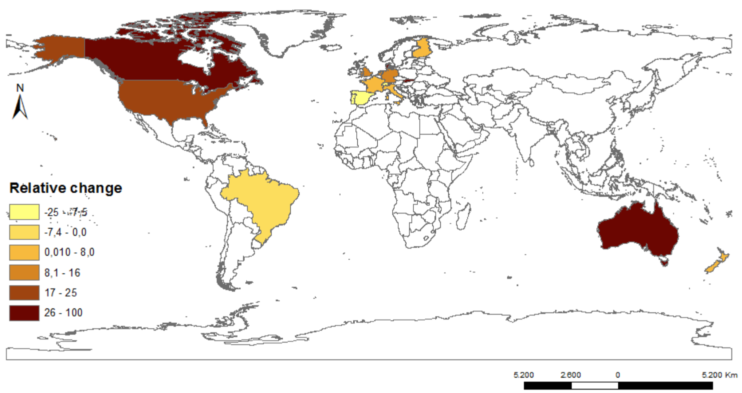

**Men 2000-2005**




**Men 2005-2010**

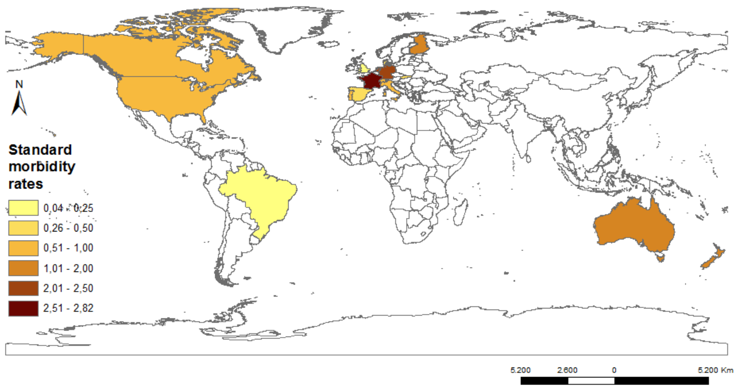



**Men 2010-20015**

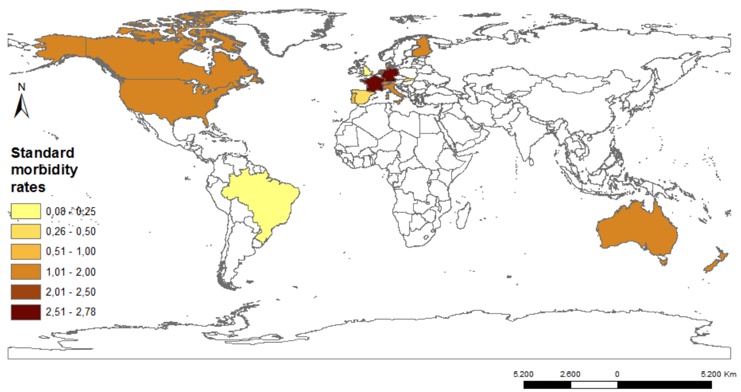


**Supplementary figure 3 – Geographic distribution of the estimated and predicted standard morbidity rates of total hip arthroplasties (95%CI) in women patient by country in 1997, 2000, 2005, 2010 and 2015**

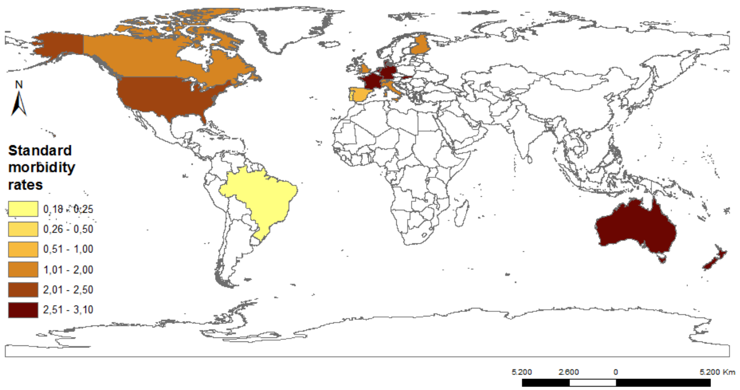
**Women 1997**



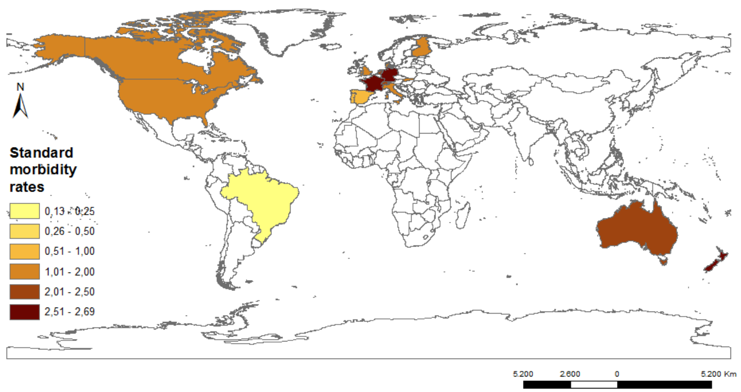

**Women 2000**



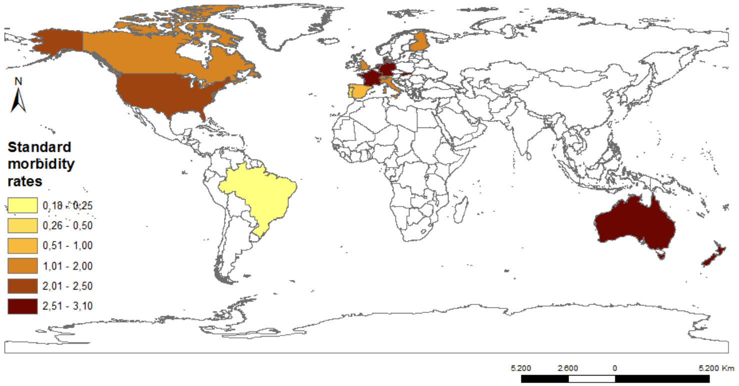

**Women 2005**




**Women 2010**

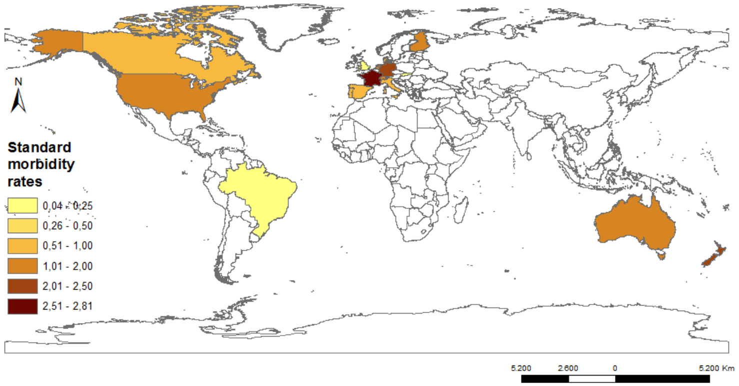


## Women 2015

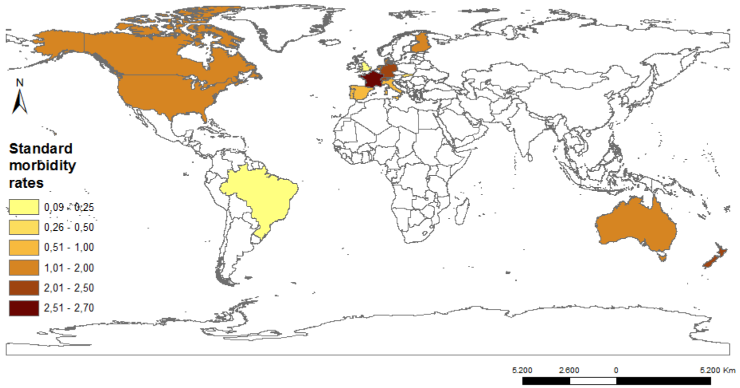

N
Standard morbidity rates
0,18 - 0,25
0,26 - 0,50
0,51 - 1,00
1,01 - 2,00
2,01 - 2,50
2,51 - 3,10
5.200
2.600
0
5.200 Km

**Supplementary figure 4 – Geographic distribution of the estimated and predicted standard morbidity rates of total hip arthroplasties (95%CI) in men patient by country in 1997, 2000, 2005, 2010 and 2015**

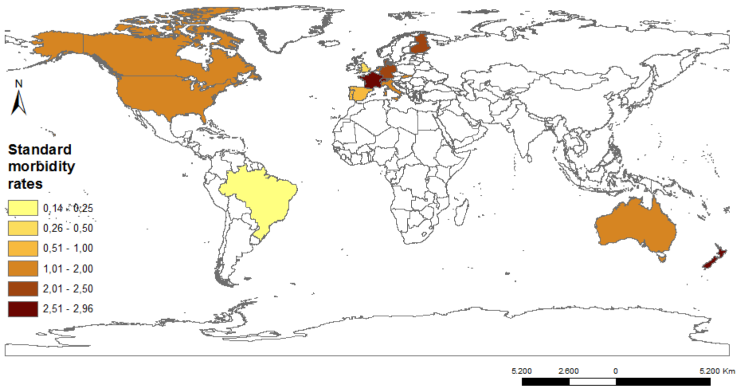
**Men 1997**



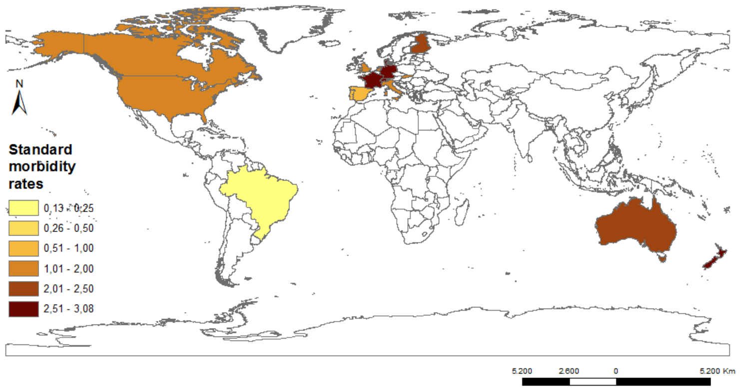

**Men 2000**



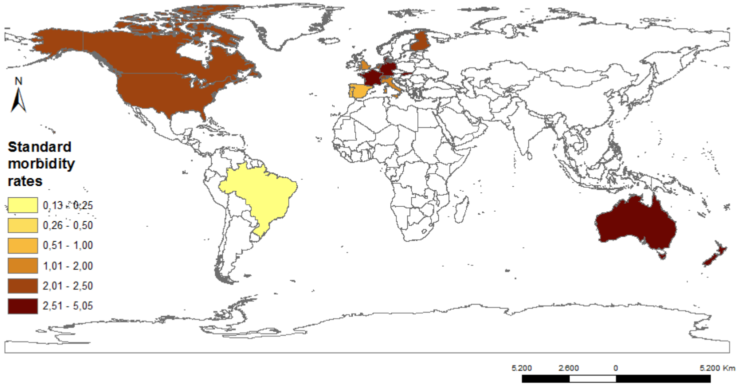

**Men 2005**




**Men 2010**



**Men 2015**


N
Standard morbidity rates
0,13 - 0,25
0,26 - 0,50
0,51 - 1,00
1,01 - 2,00
2,01 - 2,50
2,51 - 5,05
5.200
2.600
0
5.200 Km

# Chapter 4. Discussion and Conclusion

## 4.1 Discussion

A spatial and temporal variation was found in HF with a clear pattern of seasonality. The current thesis provides advances in knowledge about socioeconomic and environments factors that might explain part of the spatial and temporal variability on HF risk. It was found that socioeconomic status might explain part (but not all) of the municipalities variability of HF; CF seems to explain part of the seasonality pattern but seems not much of spatial and annually variability; and part of remain variability seems to be explained by DWC. Also, it was found that one of the most treatments used for HF, THA, showed wide differences in temporal trends between countries.

There are many factors that can affect HF risk: genetic, environmental and socioeconomic characteristics may play an important role in the pathologic process of osteoporosis. Osteoporosis is a consequence of multifactorial factors that takes place during the lifetime rather than the result of a short-time exposure. Socioeconomic, demographic and environmental context of which ones lives may influence the lifestyle, nutritional behavior and exposure to risk factors that might promote or prevent hip fracture. It is well known that exercise, nutrition, among others, is important to maintain the quality of bone mass. The maximum bone mass potential achieved by hereditary factors in the ages of bone maturation can be altered by several inadequate environmental and socioeconomic factors.

There is a great heterogeneity in HF rates between countries all over the world: it has been reported a higher incidence in countries like Scandinavia, Asia, and a lower incidence in countries near the equator. However, variability is not only been reported between countries but also, within countries and Portugal is one of these examples [14]. In Portugal, there are regions with three times higher incidences than others, higher than in some Scandinavia countries. Why do we have such high heterogeneity between municipalities? In Portugal, there are not so such high variability in genetic that can justify these differences in incidence [56-58]. Probably the context of residence areas is the main reasons for these differences. Can socioeconomic inequalities between regions or environmental factors explain part of this spatial distribution on HF incidence?

Many studies report an increase in the number of hip fracture, which is expected due to the increased life expectation that has been observed in the last decades. However, an increase in the age-adjusted incidence rates with a recent decline has been described, especially in women. The pattern of decline is clear in women but not in men and a difference between age groups has also been reported. The age-specific incidence rates seem to increase exponentially with age and the decrease in temporal trend seems to affect more women in the ages were the attention, prevention and prescription of medication and treatment against osteoporosis are higher [28]. In Portugal, we observed an increase in the absolute number of hip fracture during 2000 and 2010, however when analyzing the age-standardized incidence rates we observed two turning points: one around 2002/2003 from increase to decrease [28] and other around 2007/2008 from decrease to increase [subsection 3.1]. Why do we have the decreased between 2002/2003 and 2007/2008? Can these changes in trend be a consequence of medication prescription? Can be a consequence of a cohort effect? People that are now entered in the ages of higher HF risk are the ones that lived after the Second Word War and probably this individuals achieved a better peak bone mass in the ages of bone maturation, than their recent ancestors that lived in the Word Warn. And why does an increase was observed after 2007/2008? Can this be a reflection of the political and economic changes that has been seen after 2008 in Portugal?

In Portugal, we find also differences in trends between municipality and sexes [subsection 3.1]. For women, the age-standardized incidence rates have been decreasing in almost all of the regions, especially in littoral, north and south, although in men there is a high proportion of region where the incidence has been increasing, especially in the central interior. Why do we have these differences between regions over time (space-time)? Why is this different by sexes? Can socioeconomic inequalities explain part of this spatial-temporal distribution? Can environmental factor, such as weather or water quality explain part of this spatial-temporal distribution? Investigating reasons for changes in temporal trend and for space distribution are important to explain the differences in the incidences of HF in time and space and to identify possible modifiable factors.

Not only differences between years have been reported, but also, differences within a year (between seasons) have been described. Changes in temporal trends seem to be accompanied by seasonal changes with a higher incidence in winter. Portugal is not an exception [subsection 3.5]; we observed seasonality with a higher incidence in winter and lower in summer. Why do we have these differences between seasons? Can climatic factors explain part of this season pattern? The low temperature in winter reduce activity, increase bone loss, and worsen muscle and coordination, especially in older ages, that increase the susceptibility to falling, and consequently to fracture. Higher precipitation increases the fall risk and the low sun exposure in winter; reduce the synthesis of vitamin D, which would prevent fractures by improving musculoskeletal function and by increase the calcium homeostasis. However, when analyzing the seasonality by age group, we found that seasonality affects more the older and there is no seasonality in the younger adult (50-64 year-old) and per an increase in the age groups the seasonality becomes more pronounced [work not yet published].

We have already mentioned that the decrease in trend mentioned above, after 2002/2003, may be a consequence of changes in medical prescription. In the previous study, we have shown a clear and abrupt increase in medication against osteoporosis sales after 2003 until 2008 [59] which was in line with an intervention at the national level: the introduction of bisphosphonates as a medical recommendation against osteoporosis [60, 61]. Around 2003, it was observed a massive introduction of bisphosphonates and a decrease in the Hormone Replaces Therapy (HRT), but an overall increase of anti-osteoporotic medication [59]. We find a reduction of 10.2 (95%CI 4.8 to 15.7) fractures per 100,000 person-year per 100,000 packages sold [28]. In literature, it is described a higher reduction of HF consequence of fall prevention rather than a consequence of medication prevention. So probably fall prevention is a more cost-effective intervention than medication prescription.

Another possibility to explain this reduction may be a consequence of birth cohort effect. We found some fluctuation in the risk of hip fractures according to the year of each one’s born, and a surprising coincident with some historical political and economic changes that occurred in Portugal [32]. For instance, in 1910, with the implantation of the Portuguese republic, the quality of life improves and a reducing in the risk of hip fracture was observed in this birth cohort; then with First World War (1914-1918), the quality of life reduce and an increasing risk was observed; then with the reorganization of economy and investment in education, health and infrastructures (1933-1939), a decreasing was observed; and with the Second World War (1939-1945), an increasing risk was observed for this birth cohort. This relation should be taken with caution;

however this coincident can make some sense if we think that the quality of the bone reflects a lifetime exposure, and economic/political aspects may have some effect on the health of populations.

A possible explanation for the heterogeneity in HF risk between municipalizes might be SES. In literature is described that SES can affect the risk of hip fracture, for instance for income as a proxy for SES, it was observed a reduced risk for those with medium or high income when compared with low [62]; and a reduced risk was also observed for those with private health insurance when compared with those without [63]. In our study, we observed that the risk is lower in affluent areas when compared to deprived areas, although in the bortherline of significant for women and not significant for men [64]. However, some studies observed that SES affect in a different way per age group; for instance in age group between 40-59 years old, a reduced risk was observed for those with high school or higher education when compared with no formal schooling; and in age group higher than 60 years, an increased risk was observed for those with high school or higher education when compared with no formal schooling [65]. We found an interaction between SES and age in our study: youngest adults living in a region with high SES had a significant lower risk for HF compared to those living in lower SES and the reverse happen for oldest individuals [subsection 3.2 – [64]]. Regarding the spatial pattern before and after adjusted for SES, we observed that SES may explain part of the spatial pattern of hip fracture: a reduced risk was observed in some regions when we adjusted for SES. However, we still observed a higher incidence in some regions, such as in northwest and south of Portugal, so probably there are other factors that can explain part of the higher incidence in such regions. Can climatic factor or water quality explain part of the spatial pattern?

After the decrease period between 2002/2003 and 2007/2008 described above for Continental Portugal, an increase incidence of hip fracture has been seen after that and as mention before this can be a consequence of recession due to political and economic changes that have been observed since 2008. Experience and evidence from past recessions show a negative impact on the health of the population (not all consistency) and the magnitude of this impact depend also on the scale of the crisis, the extent to which populations are vulnerable, and government responses. However, most studies on the health effects of crisis have focused on population averages, which may obscure the potential inequalities in health due to the different population groups will be affected in different ways and inequalities tend to rise during recessions and this may be one of the reasons for not consistency of the negative impact of recessions on heath population in some studies [66]. The higher socioeconomic status is probably better at adapting to new and changing economic circumstance that the lower socioeconomic status. Regarding this point of view, we analyzed the hip incidence stratified by regional socioeconomic status to understand and monitoring differences in the temporal trend by SES, sex, and age group. We found differences in temporal trend by SES although most of the groups presented an increasing trend after 2007 (except women, 65-79 years old, in more affluent areas that show a continuous decrease). In women, in the age group where the prescription of medication and treatment against osteoporosis is higher (65-79 years-old), it seems that the decreasing trend on HF start first in the higher SES, second in the medium SES and in the lower SES an increase in the trend appears after 2007 [subsection 3.3]. The decrease in trends observed in begin of the study with different delay per SES (first in the highest and then in the medium SES), may be due to the improvement in treatment and prevention of osteoporosis observed in the recent years that affects primarily the most advantaged and the ages where the prescription of medication and treatment against osteoporosis is higher. The increasing trends in the end of the study period, for the lower SES, may reflect constraints due to political and economic changes that affect primarily the most disadvantaged especially in access to health care and treatment. Socioeconomic effect across and over time on HF risk was observed, although it seems that there is still some variability unexplained. Can climatic factor explain part of the spatial-temporal pattern of HF?

In literature, it is described that climatic factor affects the incidence of hip fracture; for instance, per an increase in mean temperature it is shown a decrease in HF risk and per an increase of hour of sunshine and day length a decrease in HF risk was observed. In Portugal, we investigated how do climatic factors affect the spatial, seasonality and annually temporal trends of HF [subsection 3.4], adjusting for the previous SES effect found [subsection 3.3]. No substantial differences in space and time were found in our study after the inclusion of CF, which means that climatic factor did not explain part of the spatial pattern and any anomaly in some year in HF; although the differential pattern was observed in seasonality. Regarding the CF effects, it seems that the direction of the association between men and women are similar. An inverse association between HF and sun duration, mean temperature, atmosphere pressure and precipitation and a direct between HF and relative humidity association were observed, however not significant for precipitation in men and for relative humidity in women.

Since climatic factor cannot explain part of the spatial pattern of hip fracture, we analyzed how does water quality affects the spatial pattern of hip fracture [subsection 3.5]. The chemical composition of drinking water composition can be associated with osteoporosis; the accumulation of mineral in the bones may contribute to their wear and consequent fragility. Some constituents of water (aluminum, arsenic, cadmium fluoride, pH, calcium, magnesium) may be prejudicial or protective to the bone, if ingested in high concentration and/or over a long period of time, increasing or decreasing the risk of osteoporosis (and consequent fracture). In literature, it was found an association between calcium ingested from drinking water and femur bone density [67]; an increased risk of HF with cadmium, lead, and aluminum [41] and a protective effect of calcium and magnesium on municipality drinking water [42]. Regarding the spatial pattern before and after adjusted for drinking water parameter and another potential confounder (such as SES), we find that the spatial pattern of HF risk seems to attenuate with the inclusion of drinking water composition, which means that water parameter may explain part of the spatial pattern of HF. There was a decreasing effect of calcium, magnesium, and iron in drinking water component on the risk of HF. We have not found a clear relation between aluminum, cadmium, color, fluoride and manganese and HF risk and this might be due to that parameter are within the acceptable and regulate values allowed. Our study seems to indicate the HF risk seems to be small around neutral pH.

Access to quality health care is a great concern for policy makers, health care and patients and a higher heterogeneity in access to health has been reported between countries. HF usually require surgical treatment period [68] with high costs to health care systems, society, and families [69]. One of the most cost-effective treatments after an HF is THA and this has been increased in almost developed countries [49-52], although the rates across countries and the velocity of changes over time greatly vary among countries [53,54]. Our study shows a higher variability between countries although with a worrying recent decrease in countries with some economic constraint [subsection 3.6]. Further investigation is a need and the underline reasons for this decrease in some countries need to be clarifying.

## 4.2 Conclusion

The research development in the current thesis shows that socioeconomic and the environmental factors might explain part of the spatial and temporal variability on HF; although it seems that is still some variability unexplained and further investigation is needed. We believe that there are other factors that can explain part of the spatial and temporal pattern of HF which should be properly explored. We believe that differences in space and time in medication and prevention intervention may explain part of these differences on HF risk and identify and monitoring this factor may help to identify possible modifiable factor and may be helpful in tailoring more effective intervention and treatment programs.

# References


1. Johnell O, Kanis JA. An estimate of the worldwide prevalence, mortality and disability associated with hip fracture. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA. 2004;15(11):897-902. Epub 2004/10/19.

2. Gallagher JC, Melton LJ, Riggs BL, Bergstrath E. Epidemiology of fractures of the proximal femur in Rochester, Minnesota. Clinical orthopaedics and related research. 1980(150):163-71. Epub 1980/07/01.

3. Hernlund E, Svedbom A, Ivergard M, Compston J, Cooper C, Stenmark J, et al. Osteoporosis in the European Union: medical management, epidemiology and economic burden. A report prepared in collaboration with the International Osteoporosis Foundation (IOF) and the European Federation of Pharmaceutical Industry Associations (EFPIA). Archives of osteoporosis. 2013;8(1-2):136. Epub 2013/10/12.

4. Dhanwal DK, Dennison EM, Harvey NC, Cooper C. Epidemiology of hip fracture: Worldwide geographic variation. Indian journal of orthopaedics. 2011;45(1):15-22. Epub 2011/01/12.

5. NIH Consensus Development Panel on Osteoporosis Prevention, Diagnosis, and Therapy, March 7-29, 2000: highlights of the conference. South Med J. 2001;94(6):569-73. Epub 2001/07/07.

6. Bischoff HA, Stahelin HB, Dick W, Akos R, Knecht M, Salis C, et al. Effects of vitamin D and calcium supplementation on falls: a randomized controlled trial. Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research. 2003;18(2):343-51. Epub 2003/02/06.

7. Morrison A, Fan T, Sen SS, Weisenfluh L. Epidemiology of falls and osteoporotic fractures: a systematic review. ClinicoEconomics and outcomes research : CEOR. 2013;5:9-18. Epub 2013/01/10.

8. Campos S AS, Carvalho M, Neves N, Trigo-Cabral A, Pina MF. Survival after a Proximal Femur Fracture: 252 patients followed during one-year after the fracture. Submitted to Acta orthopaedica – under review. 2013.

9. Koval KJ, Skovron ML, Aharonoff GB, Zuckerman JD. Predictors of functional recovery after hip fracture in the elderly. Clinical orthopaedics and related research. 1998(348):22-8. Epub 1998/04/29.

10. The prevention of falls in later life. A report of the Kellogg International Work Group on the Prevention of Falls by the Elderly. Danish medical bulletin. 1987;34 Suppl 4:1-24. Epub 1987/04/01.

11. Cheng SY, Levy AR, Lefaivre KA, Guy P, Kuramoto L, Sobolev B. Geographic trends in incidence of hip fractures: a comprehensive literature review. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA. 2011;22(10):2575-86. Epub 2011/04/13.

12. Pina MF, Alves SM, Barbosa M, Barros H. Hip fractures cluster in space: an epidemiological analysis in Portugal. Osteoporos Int. 2008.

13. Johnell O, Gullberg B, Allander E, Kanis JA. The apparent incidence of hip fracture in Europe: a study of national register sources. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA. 1992;2(6):298-302. Epub 1992/11/01.

14. de Pina MF, Alves SM, Barbosa M, Barros H. Hip fractures cluster in space: an epidemiological analysis in Portugal. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA. 2008;19(12):1797-804. Epub 2008/06/10.

15. West J, Hippisley-Cox J, Coupland CA, Price GM, Groom LM, Kendrick D, et al. Do rates of hospital admission for falls and hip fracture in elderly people vary by socio-economic status? Public Health. 2004;118(8):576-81. Epub 2004/11/09.

16. Kannus P, Niemi S, Parkkari J, Palvanen M, Vuori I, Jarvinen M. Nationwide decline in incidence of hip fracture. J Bone Miner Res. 2006;21(12):1836-8.

17. Chevalley T, Guilley E, Herrmann FR, Hoffmeyer P, Rapin CH, Rizzoli R. Incidence of hip fracture over a 10-year period (1991-2000): reversal of a secular trend. Bone. 2007;40(5):1284-9. Epub 2007/02/13.

18. Abrahamsen B, Vestergaard P. Declining incidence of hip fractures and the extent of use of anti-osteoporotic therapy in Denmark 1997-2006. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA. 2010;21(3):373-80. Epub 2009/05/14.

19. Nilson F, Moniruzzaman S, Gustavsson J, Andersson R. Trends in hip fracture incidence rates among the elderly in Sweden 1987-2009. J Public Health (Oxf). 2013;35(1):125-31. Epub 2012/07/04.

20. Korhonen N, Niemi S, Parkkari J, Sievanen H, Palvanen M, Kannus P. Continuous decline in incidence of hip fracture: nationwide statistics from Finland between 1970 and 2010. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA. 2013;24(5):1599-603. Epub 2012/10/31.

21. Omsland TK, Holvik K, Meyer HE, Center JR, Emaus N, Tell GS, et al. Hip fractures in Norway 1999-2008: time trends in total incidence and second hip fracture rates: a NOREPOS study. European journal of epidemiology. 2012;27(10):807-14. Epub 2012/08/09.

22. Maravic M, Taupin P, Landais P, Roux C. Change in hip fracture incidence over the last 6 years in France. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA. 2011;22(3):797-801. Epub 2010/06/03.

23. Arias LH, Treceno C, Garcia-Ortega P, Rodriguez-Paredes J, Escudero A, Sainz M, et al. Hip fracture rates and bisphosphonate consumption in Spain. An ecologic study. European journal of clinical pharmacology. 2013;69(3):559-64. Epub 2012/07/24.

24. Lippuner K, Popp AW, Schwab P, Gitlin M, Schaufler T, Senn C, et al. Fracture hospitalizations between years 2000 and 2007 in Switzerland: a trend analysis. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA. 2011;22(9):2487-97. Epub 2010/12/15.

25. Hartholt KA, Oudshoorn C, Zielinski SM, Burgers PT, Panneman MJ, van Beeck EF, et al. The epidemic of hip fractures: are we on the right track? PloS one. 2011;6(7):e22227. Epub 2011/07/30.

26. Mann E, Icks A, Haastert B, Meyer G. Hip fracture incidence in the elderly in Austria: an epidemiological study covering the years 1994 to 2006. BMC geriatrics. 2008;8:35. Epub 2008/12/25.

27. Lyritis GP, Rizou S, Galanos A, Makras P. Incidence of hip fractures in Greece during a 30-year period: 1977-2007. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA. 2013;24(5):1579-85. Epub 2012/10/16.

28. Alves SM, Economou T, Oliveira C, Ribeiro AI, Neves N, Gomez-Barrena E, et al. Osteoporotic hip fractures: bisphosphonates sales and observed turning point in trend. A population-based retrospective study. Bone. 2013;53(2):430-6. Epub 2013/01/01.

29. Icks A, Haastert B, Wildner M, Becker C, Meyer G. Trend of hip fracture incidence in Germany 1995-2004: a population-based study. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA. 2008;19(8):1139-45. Epub 2007/12/19.

30. Feder G, Cryer C, Donovan S, Carter Y. Guidelines for the prevention of falls in people over 65. The Guidelines' Development Group. Bmj. 2000;321(7267):1007-11. Epub 2000/10/20.

31. Melton LJ, 3rd, Kanis JA, Johnell O. Potential impact of osteoporosis treatment on hip fracture trends. J Bone Miner Res. 2005;20(6):895-7. Epub 2005/05/11.

32. Alves SM, Castiglione D, Oliveira CM, de Sousa B, Pina MF. Age-period-cohort effects in the incidence of hip fractures: political and economic events are coincident with changes in risk. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA. 2014;25(2):711-20. Epub 2013/08/29.

33. Tenias JM, Estarlich M, Fuentes-Leonarte V, Iniguez C, Ballester F. Short-term relationship between meteorological variables and hip fractures: an analysis carried out in a health area of the Autonomous Region of Valencia, Spain (1996-2005). Bone. 2009;45(4):794-8. Epub 2009/07/01.

34. Muir SW, Montero-Odasso M. Effect of vitamin D supplementation on muscle strength, gait and balance in older adults: a systematic review and meta-analysis. J Am Geriatr Soc. 2011;59(12):2291-300. Epub 2011/12/23.

35. Anderson PH, Turner AG, Morris HA. Vitamin D actions to regulate calcium and skeletal homeostasis. Clin Biochem. 2012. Epub 2012/03/15.

36. Tucker P, Gilliland J. The effect of season and weather on physical activity: a systematic review. Public Health. 2007;121(12):909-22. Epub 2007/10/09.

37. Bulajic-Kopjar M. Seasonal variations in incidence of fractures among elderly people. Inj Prev. 2000;6(1):16-9. Epub 2000/03/23.

38. Aaseth J, Boivin G, Andersen O. Osteoporosis and trace elements--an overview. J Trace Elem Med Biol. 2012;26(2-3):149-52. Epub 2012/05/12.

39. Alffram PA, Hernborg J, Nilsson BE. The influence of a high fluoride content in the drinking water on the bone mineral mass in man. Acta orthopaedica Scandinavica. 1969;40(2):137-42. Epub 1969/01/01.

40. Simon MJ, Beil FT, Ruther W, Busse B, Koehne T, Steiner M, et al. High fluoride and low calcium levels in drinking water is associated with low bone mass, reduced bone quality and fragility fractures in sheep. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA. 2014;25(7):1891-903. Epub 2014/04/30.

41. Dahl C, Sogaard AJ, Tell GS, Flaten TP, Hongve D, Omsland TK, et al. Do cadmium, lead, and aluminum in drinking water increase the risk of hip fractures? A NOREPOS study. Biological trace element research. 2014;157(1):14-23. Epub 2013/11/30.

42. Dahl C, Sogaard AJ, Tell GS, Flaten TP, Hongve D, Omsland TK, et al. Nationwide data on municipal drinking water and hip fracture: could calcium and magnesium be protective? A NOREPOS study. Bone. 2013;57(1):84-91. Epub 2013/07/09.

43. He YF, Ma Y, Gao C, Zhao GY, Zhang LL, Li GF, et al. Iron overload inhibits osteoblast biological activity through oxidative stress. Biological trace element research. 2013;152(2):292-6. Epub 2013/01/22.

44. Lareau C, Sawyer G. Hip fracture surgical treatment and rehabilitation. Medicine and health, Rhode Island. 2010;93(4):108-11. Epub 2010/05/22.

45. Wilson NA, Schneller ES, Montgomery K, Bozic KJ. Hip and knee implants: current trends and policy considerations. Health Aff (Millwood). 2008;27(6):1587-98. Epub 2008/11/11.

46. Mahomed NN, Barrett JA, Katz JN, Phillips CB, Losina E, Lew RA, et al. Rates and outcomes of primary and revision total hip replacement in the United States medicare population. The Journal of bone and joint surgery American volume. 2003;85-A(1):27-32. Epub 2003/01/21.

47. Hawker GA, Wright JG, Glazier RH, Coyte PC, Harvey B, Williams JI, et al. The effect of education and income on need and willingness to undergo total joint arthroplasty. Arthritis and rheumatism. 2002;46(12):3331-9. Epub 2002/12/17.

48. Chaturvedi N, Ben-Shlomo Y. From the surgery to the surgeon: does deprivation influence consultation and operation rates? The British journal of general practice : the journal of the Royal College of General Practitioners. 1995;45(392):127-31. Epub 1995/03/01.

49. Dixon T, Shaw M, Ebrahim S, Dieppe P. Trends in hip and knee joint replacement: socioeconomic inequalities and projections of need. Annals of the rheumatic diseases. 2004;63(7):825-30. Epub 2004/06/15.

50. Puolakka TJ, Pajamaki KJ, Halonen PJ, Pulkkinen PO, Paavolainen P, Nevalainen JK. The Finnish Arthroplasty Register: report of the hip register. Acta orthopaedica Scandinavica. 2001;72(5):433-41. Epub 2001/12/01.

51. Wells VM, Hearn TC, McCaul KA, Anderton SM, Wigg AE, Graves SE. Changing incidence of primary total hip arthroplasty and total knee arthroplasty for primary osteoarthritis. The Journal of arthroplasty. 2002;17(3):267-73. Epub 2002/04/09.

52. Jimenez-Garcia R, Villanueva-Martinez M, Fernandez-de-Las-Penas C, Hernandez-Barrera V, Rios-Luna A, Garrido PC, et al. Trends in primary total hip arthroplasty in Spain from 2001 to 2008: evaluating changes in demographics, comorbidity, incidence rates, length of stay, costs and mortality. BMC musculoskeletal disorders. 2011;12:43. Epub 2011/02/11.

53. Pina M, Ribeiro A, Santos C. European Instructional Lectures: 12th EFORT Congress Copenhagen, Denmark. 2011;11:9-19.

54. Merx H, Dreinhofer K, Schrader P, Sturmer T, Puhl W, Gunther KP, et al. International variation in hip replacement rates. Annals of the rheumatic diseases. 2003;62(3):222-6. Epub 2003/02/21.

55. ACSS. Auditoria da codificação clínica [Clinical codification Audits]. 2011 Available from: http://portalcodgdh.min-saude.pt/index.php/Auditoria_da_codificação_cl%C3%ADnica.

56. Pereira L, Prata M, Amorim A. Diversity of mtDNA lineages in Portugal: not a genetic edge of European variation. Ann Hum Genet. 2000;64:491-506.

57. Pereira R, Fondevila M, Philips C, Amorim A, Carracedo A, Gusmao L. Genetic characterization of 52 autosomal SNPs in the Portuguese population. Forensic Science International, Genetics Supplement Series. 2008;1:358-60.

58. Beleza S, Gusmao L, Lopes A. Micro-phylogeographic and demographic history of Portuguese male lineages. Ann Hum Genet. 2006;70:181-94.

59. Alves SM, Economou T, Oliveira C, Ribeiro AI, Neves N, Gomez-Barrena E, et al. Osteoporotic hip fractures: Bisphosphonates sales and observed turning point in trend. A population-based retrospective study. Bone. 2012. Epub 2013/01/01.

60. SPR S. Recomendações para o Diagnóstico e Terapêutica da Osteoporose. Acta Reumatol Port 2007;32:49-59.

61. DGS. Tratamento Farmacológico da Osteoporose Pós-menopaúsica. Lisboa. 2011.

62. Farahmand BY, Persson PG, Michaelsson K, Baron JA, Parker MG, Ljunghall S. Socioeconomic status, marital status and hip fracture risk: a population-based case-control study. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA. 2000;11(9):803-8. Epub 2001/01/10.

63. Peel NM, McClure RJ, Hendrikz JK. Psychosocial factors associated with fall-related hip fractures. Age and ageing. 2007;36(2):145-51. Epub 2007/01/30.

64. Oliveira CM, Economou T, Bailey T, Mendonca D, Pina MF. The interactions between municipal socioeconomic status and age on hip fracture risk. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA. 2015;26(2):489-98. Epub 2014/10/26.

65. Vestergaard P, Rejnmark L, Mosekilde L. Socioeconomic aspects of fractures within universal public healthcare: a nationwide case-control study from Denmark. Scandinavian journal of public health. 2006;34(4):371-7. Epub 2006/07/25.

66. Suhrcke M, Stuckler D, Leone T. Recession and health in Europe: what to expect? The London School of Economic and Political Science. 2009.

67. Aptel I, Cance-Rouzaud A, Grandjean H. Association between calcium ingested from drinking water and femoral bone density in elderly women: evidence from the

EPIDOS cohort. Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research. 1999;14(5):829-33. Epub 1999/05/13.

68. Alfven T, Elinder CG, Hellstrom L, Lagarde F, Jarup L. Cadmium exposure and distal forearm fractures. J Bone Miner Res. 2004;19(6):900-5. Epub 2004/05/06.

69. Burge R, Dawson-Hughes B, Solomon DH, Wong JB, King A, Tosteson A. Incidence and economic burden of osteoporosis-related fractures in the United States, 2005-2025. Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research. 2007;22(3):465-75. Epub 2006/12/06.